Journal of NeuroVirology (2000) 6, Suppl 2, S141–S146

www.jneurovirol.com

Exogeneous factors in the aetiology of multiple sclerosis

Enrico Granieri*,[1]

[1]*Multiple Sclerosis Center, Department of Neurology, University of Ferrara, Ferrara, Italy*

Neuroepidemiology has undoubtedly played a fundamental role in the study of multiple sclerosis (MS) by providing some aetiologic clues, although a definitive basis for the conclusive resolution of its enigma is still lacking. Epidemiological and genetic studies have indicated that MS is probably caused by multiple factors, both genetic and environmental, none of which is individually sufficient, which appear to act before adolescence – or possibly later – in genetically susceptible individuals. This unifying hypothesis emphasizes, on the one hand, the role of a genetic-racial susceptibility and the importance of environmental factors and, on the other, a possible aetiologic heterogeneity and lack of specificity of the unknown endogenous and exogeneous agents. In this context, several environmental factors may be involved in the aetiopathogenesis of MS in individuals who are susceptible to the effect of exposure to these factors. Situations or events with biological plausibility, such as childhood or adolescent infectious diseases, exposures to geographic and socio-cultural factors, nutritional habits, hypersensitivity, significant head and spinal trauma, and other factors may contribute, at different times, to the putative acquisition of MS, trigger its onset, and modify its subsequent course. However, additional empirical evidence is needed to clarify the complex interplay of genetic and environmental factors. *Journal of NeuroVirology* (2000) **6,** S141–S146.

Keywords: multiple sclerosis; epidemiology; environment; risk factors; socio-cultural factors; latitude

The aetiology of multiple sclerosis (MS) remains unclear. Nevertheless, the scientific data which have emerged from genetic and epidemiological studies have provided us with some consistent findings.

Evidence is emerging for the involvement of genetic factors: differences in frequency among races; existence of resistant groups or populations, familial studies; concordant rates for MS twin pairs; associations with some proposed susceptibility genes.

The possible role of environment in MS aetiology has been demonstrated by the different geographic gradients of frequency, changes in incidence and prevalence among Caucasians; changes in prevalence in migrants and effects of age at migration; possible 'epidemics' and clusters of cases in some little communities; less than complete concordance in twin studies (Ebers, 1995).

*Correspondence: E Granieri, Sezione di Clinica Neurologica, Dipartimento di Discipline Medico-Chirurgiche della Comunicazione e del Comportamento, Università di Ferrara, Corso della Giovecca 203, I-44100 Ferrara, Italy

Both racial–genetic and environmental factors are involved in the aetiopathogenesis of MS. It is likely that each of the endogeneous genetic factors, which induce host susceptibility, differs in its dynamics of procedures, when environment is favourable to this in an adequate age of host. In the same way, several physical, biological and socio-economic environmental factors may be involved in the aetiopathogenesis of MS in individuals who are susceptible to the effects of these factors. Moreover, these factors may contribute, at different times, to the putative acquisition of MS, trigger its onset and modify the subsequent course of the disease (Granieri, 1997; Compston, 1998).

For many years MS has been considered a disease which is strongly influenced by infectious agents, but this hypothesis is still bluffed by the lack of evidence for specific virus and the weakness of the results of analytical studies which test associations between MS and previous infections (Compston, 1998; Casetta and Granieri, 2000).

The role of other environmental factors are greatly considered in aetiologic studies (Table 1).

Table 1 Environmental risk factors that increase susceptibility to multiple sclerosis.

Geographic factors
Latitude
Climate
Altitude
Physical and chemical agents
Land usage
Socio-cultural factors
Socio-economic factors
Industrialization and modernization
Living in urban areas
Religious practices
Hygienic and sanitary conditions
Diet and nutritional habits
Working occupation and exposures to:
– infectious agents,
– farmed animals,
– organic solvents,
– trauma
Biological risk factors
Infectious agents, virus in particular
Vaccinations
Trauma
Surgical operations
Stress
Pregnancy

Geographical correlations

Ecologic geographic investigations offer interesting leads. Investigators have found correlations of MS frequency with climate (low temperature and winter dampness), in mountainous terrains and exposure to radiations, geochemical formations (soils rich in heavy metals, clay and peats). Correlations have been suggested with land usage (agriculture, grazing, coniferous forests) and with industrialized and urbanized areas. For the ecological correlations these could be biologically possible explanations: Low temperature and high level of humidity may have direct effects on the immune system or may be conducive to frequent respiratory tract infections; lack of winter sunlight influences vitamin D levels, but also stress level and biological clock, and therefore there may be effects on the immune system (Lauer, 1995, 1999). Substances in soils, such as aromatic compounds, resins, organic solvents, used in industry, may alter endogeneous proteins which are recognized by the immune system and stimulate the immune responses. Land usage and changes in modernization and industrialization may influence lifestyle, socioeconomic status, diet, exposure to animals. These and other associations have either been confirmed or rejected in studies, most of which were not independent of the effects of latitude (Lauer, 1995, 1999).

Animal exposure, and consequently exposure to animal infections, have been extensively studied with ecological and retrospective case-control investigations. The analyses of the studies, different in methodologies, have in general revealed no consistent associations between MS and domestic and/or farm animals (Hodge and Wolfson, 1997). The putative association in northern Europe with canine distemper virus – possibly responsible for acute demyelination – could be ecologically related to predilection of MS for cold and humid environments of countries in high latitudes (Lauer, 1999).

Working activities

Occupation, which itself has consistence with local socio-economic factors and changes in industrialization and modernization, may also be a risk factor for MS. In some studies in the UK and Germany a higher than expected proportion of MS patients was found in professional, technical, and administrative occupational groups at onset of the disease as compared with those in other categories of employment. However, other reports from Israel, the US and Spain did not confirm this finding (Granieri, 1999). Professional contacts of young nurses with MS patients and employment as hairdressers have both been suggested as working risks. However, most studies have not provided conclusive evidence of risks involved in these or other jobs (Weinshenker and Rodriguez, 1995).

Correlations between MS and exposures to organic solvents have been investigated. Continuative exposures to organic solvents could promote effects on the disease through damage to the blood-brain-barrier, opening it to infectious or other noxious agents (Poser, 1994). The risk ratios of analytical studies are generally positive, but the different methodologies among the surveys do not permit easy comparability (Landtblom, 1997).

Diet and nutrition

Although the association between food and risk for MS is one of the most investigated aspects of the disease, potential correlations which have emerged from analytical studies remain controversial. The distribution of animal fat consumption, meat in particular, has been found to be associated with MS frequency in some studies (Ebers, 1995). Most case-control studies show a distinct increase in MS risk, in particular when fat intake during childhood is taken into account. Meat consumption is consistently associated with MS risk, but typically only in countries or areas in which MS frequency is high (Lauer, 1999). Few case-control surveys show any link between the disease and a diet which is rich in meat. The consumption of dairy foods associated with MS risk seems to be well documented in ecological studies, whereas it is less evaluable in case-control investigations (Lauer, 1997). Eating

smoked meat, with or without curing beforehand, shows an association with MS. Some case-control studies implicate consumption of nitrate-cured meats during childhood.

The effects of non-animal vegetable fats or fish fats as protective factors is not well documented. However, it may reflect a real protective effect. Omega-6 fat acids, common in fish oils, seems to reduce the severity of relapses, and addition in the diet of Omega-3 fatty acids seems to increase this beneficial effect. Further investigations are warranted (Lauer, 1999).

Other dietary factors, such as cereals, oats, grain containing gluten, vitamin A, D and E levels, calcium and selenium, are still under investigation.

Socio-cultural aspects

Changes in modernization and industralization, living in rural/urban areas, hygienic and sanitary conditions, social and economic status of people and other socio-cultural differences in lifestyle, including religious practices in some communities, may influence the epidemiology of MS and may be determinants of risk (Ebers, 1995).

Various studies across the European and American immigrants to Israel have supported the idea that people of higher socio-economic classes tend to be more likely to develop MS if compared with the average population data (Granieri, 1999). High prevalence ratios of MS among subjects with a higher educational level have been found in recent reports, the latest being from Australia in 1996 (Hammond *et al*, 1996). Educational level can give a measure of overall status.

The possible role of socio-economic factors has also been investigated through case-control studies (Granieri, 1999). Old and recent analyses of the veteran cohort in the US continue to draw attention to higher socio-economic status as a risk factor for MS. Kurtzke and Page (1997) have found a positive correlation among whites and black women. However, some investigators suggest that this complex analysis may be exposed to confounding effects of geographic, socio-cultural and ethnic variables (Lowis, 1990).

MS frequency can be correlated with the levels of sanitation and hygiene, with environments where sanitary standards are high or improved as has been noted in numerous studies (Ebers, 1995; Granieri, 1999). However in general, care has not been taken to distinguish between socio-cultural and hygienic conditions during childhood and adolescence and MS onset. A recent case control study carried out in Israel have shown that MS patients tended to have higher socio-cultural status than controls during childhood (Zilber and Kahana, 1996). Probably a protective effect of poor sanitary conditions and low socio-economic status against MS risk have been present only when living conditions were well below average, as is frequent in developing countries, where MS is rare. Better sanitation among socio-economic and cultural factors correlates positively with the higher frequency on MS. The theory that MS is an immune response to delayed occurrence of common childhood infections could explain the lower incidence of MS among children with low socio-economic level, who are, in general, infected earlier (Poskanzer *et al*, 1980). Cleanliness seems to play an important role in the development of experimental autoimmune diseases (Leiter *et al*, 1990).

The evidence of differences in MS risk for individuals born or living in urban or rural areas has produced conflicting results. Residence in large centres at birth and at the time of entry into the Armed Forces was associated with a fourfold increase in risk of MS in the US veteran studies (Beebe *et al*, 1967). Higher frequency was also found in Israel, and Western Australia, but not in other countries (Compston, 1998). It is difficult to draw any conclusions, because of methodological differences in the studies. However, the strong association of MS risk with urban residence found in the last US veteran case-control study (Kurtzke and Page, 1997) seems to have eliminated sources of bias. MS may be associated with changes in lifestyle paralleled with the processes of urbanization and technological development in the area of residence during the age at risk.

Socio-cultural changes related to modernization and Westernization can be a useful gauge in studying the changes in incidence rates of MS found in previous isolated communities. Sardinia is one such example, where a growing trend in the incidence of MS has been detected in recent years. Having lost their geographical isolation after the Second World War, the Sardinian people have been increasingly exposed to new environmental factors: growing contact with the Continent, variations in the way of life and diet, tendency to urbanization, improvement in economic status, in hygiene and sanitation – including campaigns of vaccination and possible delay in acquiring childhood diseases. The incidence of MS in Sardinia is much higher than the rest of Italy, with a dramatic increase in rates in the last three decades (Granieri *et al*, 1998). Genetic and historical data strongly suggest a role of environmental and genetic factors in determining the notable difference in MS risk between Sardinians and the rest of Italy. The Sardinians are an ethnically homogeneous population, having a genetic structure which is quite different from that of all other Italian and European populations (Compston, 1998). A very similar temporal pattern to that of MS has been observed for juvenile diabetes: incidence rates of this autoimmune disease in Sardinia are now the second highest in Europe (Muntoni *et al*, 1992). This is attributed, at

least in part, to changes related to modernization and Westernization that have occurred on the island since World War II.

Vaccination

Despite a number of notifications of MS cases in temporal associations with some vaccinations, such as antidiphtheria, rabies, polio, rubella and influenza, the possible risk of immunization in the aetiopathogenesis of the disease remains unclear (Ebers, 1998). Retrospective studies have led to conflicting results (Table 2). Most studies considered vaccinations as exposures which occurred prior to the disease onset, without evaluating the possible temporal relationship between vaccination and MS appearance (Sibley, 1986). In addition, given the retrospective nature of these studies, information has been collected so long after the event that it is no longer completely reliable (Granieri, 1999). Vaccination can produce the classical post vaccine encephalitis; vaccine may stimulate the appearance of MS in genetically predisposed subjects (Rosati, 1990; Fenichel, 1999).

In recent years concerns have also been raised that Hepatitis B vaccine may be related to new cases or exacerbations of MS, as well as other demyelinating diseases. Cases of demyelination involving the Central Nervous System following immunization with recombinant vaccine have been published (Grotto *et al*, 1996). However, in the case of MS in temporal correlation with Hepatitis B immunization, the results, at present, do not provide definitive evidence of a causal link. Surveillance data on cases of demyelinating diseases following vaccination are compatible with the expected incidence of MS (WHO, 1997).

Trauma

A possible relationship between traumas and MS has been suggested from time to time by anedoctical observations of unique cases or revisions of clinical series. Today the presumed associations between trauma and MS is based on nearly ten case-control studies and the recent population-based study of a cohort in Olmsted County (Siva *et al*, 1993; Compston, 1998). The studies have furnished contradictory results, and the problem of the possible pathogenetic role of trauma at the beginning and during the clinical course of MS remains unsolved. An attempt to improve the quality of studies on this putative risk factor, by better definitions and selection of the various types of traumas (head trauma, spinal trauma, others, surgical operations, ...) would be opportune. In particular, it would be interesting to focalize attention on traumas which can determinate transitory damage of the blood–brain–barrier (Poser, 1994). On the other hand, opening of the blood brain barrier is necessary, but not sufficient to establish the cascade of events which culminate in demyelination (Compston, 1998).

A recent statement of the relationship of MS to physical trauma has been provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. 'On the basis of strong and generally consistent evidence provided by well designed clinical studies (case-control and cohort studies), any posited association of physical trauma, expecially head trauma, with more than a small effect on either MS onset or MS exacerbation is excluded. Moreover, the preponderance of the epidemiological studies supports no association between physical trauma and either MS onset or MS exacerbation' (Goodin *et al*, 1999).

Table 2 Results of some case-control studies on vaccinations.

Authors	*Year published*	*Results*
Alter and Speer	1968	Lower frequency of diphtheria inoculation. Higher percentages of smallpox, influenza and BCG, and lower percentages of tetanus, pertussis, polio, typhoid vaccinations (n.s.)
Cendrowski *et al*	1969	Higher frequency of hyperergic reactions
Currier *et al*	1974	Vaccinations recorded less often by patients, including smallpox, diphtheria-pertussis, BCG, polio, tetanus. More reactions to immunization in cases*
Andersen *et al*	1981	No associations
Berr *et al*	1989	No differences in vaccinations against polio and tbc. Data about other vaccinations not recorded. Age at the time of immunization significantly higher in cases
Hopkins *et al*	1991	Association with oral polio vaccine
Lauer and Firnhaber	1994	No associations
Casetta *et al*	1994	No associations
Milonas	1994	No associations
Zilber and Kahana	1996	Significantly more patients were vaccinated against typhoid, and fewer patients against tetanus. A significant negative association was found between MS and Sabin polio vaccination
Kurtzke *et al*	1997	Vaccination for smallpox, tetanus, and diphtheria less common in cases. In general MS cases tend to be undervaccinated

*In two cases the first MS symptom occurred in temporal association with vaccination

Conclusion

The complexity and variability of the aetiological studies, together with methodological differences and, in some cases, weakness in the biological plausibility of some putative risk factor investigated, make it difficult to draw any conclusions. On the other hand, there is evidence for the involvement of environmental exposures in the aetiology and progression of MS. Moreover, the failure of an epidemiological study to detect an association does not mean that the link may not exist. Better methodology and collaboration with other investigators involved in the fields of genetics, virology, immunology, hygiene science, etc., must be developed if research is to continue to provide more clues in order to unravel the complexity involved in MS aetiology.

References

Alter M, Speer J (1968). Clinical evaluation of possible aetiologic factors in multiple sclerosis. *Neurology* **18:** 109–116.

Andersen E, Isager H, Hyllested K (1981). Risk factors in multiple sclerosis: tubercolin reactivity, age at measle infection, tonsillectomy and appendicectomy. *Acta Neurol Scand* **63:** 131–135.

Beebe GW, Kurtzke JF, Kurland LT, Auth TL, Nagler B (1967). Studies on the natural history of multiple sclerosis. III. Epidemiologic analysis of the army experience in World War II. *Neurology* **17:** 1–17.

Berr C, Puel J, Clanet M, Ruidavets JB, Mas JL, Alperovitch A (1989). Risk factors in multiple sclerosis: a population-based case-control study in Hautes-Pyrénées, France. *Acta Neurol Scand* **80:** 46–50.

Casetta I, Granieri E, Malagù S, Tola MR, Paolino E, Caniatti LM, Govoni V, Monetti VC, Fainardi E (1994). Environmental risk factors and multiple sclerosis: a communoity-based, case-control study in the province of Ferrara, Italy. *Neuroepidemiology* **13:** 120–127.

Casetta I, Granieri E (1999). Clinical infections and multiple sclerosis: Contribution from analytical epidemiology. *J Neurovirol* **6** (suppl 2): S147–S151.

Cendrowski W. Wender M, Dominik K, Flejsierowicz Z, Owsianowski M, Popiel M (1969). Epidemiological study of multiple sclerosis in western Poland. *Eur Neurol* **2:** 90–108.

Compston DAS (1998). Genetic epidemiology. In: *McAlpine's Multiple Sclerosis*. 3rd edn. Compston DAS, Ebers G, Lassmann H, McDonald I, Matthews B, Wekerle H (eds). Churchill Livingstone: London, Edinburgh, New York, Philadelphia, Sydney, Toronto, pp 45–142.

Currier RD, Martin EA, Woosley PC (1974). Prior events in multiple sclerosis. *Neurology* **24:** 748–754.

Ebers G (1995). *Multiple sclerosis. Epidemiology and etiology.* Shering AG (ed). Educational Service, Berlin, 1995.

Ebers G (1998). Natural history of multiple sclerosis. In: *McAlpine's Multiple Sclerosis*. 3rd edn. Compston DAS, Ebers G, Lassmann H, McDonald I, Matthews B, Wekerle H (eds). Churchill Livingstone: London, Edinburgh, New York, Philadelphia, Sydney, Toronto, pp 191–221.

Fenichel GM (1999). Assessment: Neurologic risk of immunization. *Neurology* **52:** 1546–1552.

Goodin DS, Ebers GC, Johnson KP, Rodriguez M, Sibley WA, Wolinsky JS (1999). The relationship to physical trauma and psychological stress: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **52:** 1737–1345.

Granieri E (1997). The epidemiologic study of exogenous factors in the etiology of multiple sclerosis. *Introduction. Neurology* **49** (suppl 2): S2–S3.

Granieri E, Casetta I, Tola MR, Lauria G, Murgia SB, Ticca A, Marchi D, Murgia B, Pugliatti M, Sotgiu S, Rosati G (1998). Incidence trend of multiple sclerosis in two Italian populations. *Multiple Sclerosis* **4:** 519.

Granieri E (1999). Socio-cultural aspects of multiple sclerosis. In: *Environmental Factors in Multiple Sclerosis*. Ebers G (ed). 10th MS Forum Modern Management Workshop, Schering AG, Educational Service, Berlin, Germany: 6–9.

Grotto I, Mandel Y, Ephros M, Ashkenazi I, Shemer J (1996). Major adverse reactions to yeast-derived hepatitis B vaccines–a review. *Vaccine* **16:** 329–334.

Hammond SR, McLeod JG, Macaskill P, English D (1996). Multiple sclerosis in Australia: Socio-economic factors. *J Neurol Neurosurg Psychiatry* **61:** 311–313.

Hodge MJ, Wolfson C (1997). Canine distemper virus and multiple sclerosis. *Neurology* **49** (Suppl 2): S62–S69.

Hopkins RS, Indian RW, Pinnow E, Conomy J (1991). Multiple sclerosis in Galion, Ohio: prevalence and results of a case-control study. *Neuroepidemiology* **10:** 192–199.

Kurtzke JF, Page WF (1997). Epidemiology of multiple sclerosis in US veterans. VII. Risk factors. *Neurology* **48:** 204–213.

Kurtzke JF, Hyllested K, Arbuckle JD, Bronnum-Hansen H, Wallin MT, Heltberg A, Jacobsen H, Olsen A, Eriksen LS (1997). Multiple sclerosis in in the Faroe Islands. 7. Results of a case-control questionnaire with multiple controls. *Acta Neurol Scand* **96:** 149–157.

Landtblom AM (1997). Exposure to organic solvents and multiple sclerosis. *Neurology* **49** (suppl 2): S70–S74.

Lauer K, Firnhaber W (1994). Descriptive and analytical epidemiological data on multiple sclerosis from a long-term study in southern Hesse, Germany. In: *Multiple Sclerosis in Europe. An epidemiological update*. Lauer K, Firnhaber W (eds). Alsbach-Bergstrasse: Leuchtturm-Verlag/LTV Press, pp 147–158.

Lauer K (1995). Environmental associations with the risk of multiple sclerosis: the contribution of ecological studies. *Acta Neurol Scand* **91** (suppl 161): 77–81.

Lauer K (1997). Diet and multiple sclerosis. *Neurology* **49** (suppl 2): S55–S61.

Lauer K (1999). Ecological features of multiple sclerosis. In: *Environmental Factors in Multiple Sclerosis*. Ebers G (ed). 10th MS Forum Modern Management Workshop, Schering AG, Educational Service, Berlin, Germany: 1–5.

Leiter EH, Serreze DV, Prochazka M (1990). The genetics and epidemiology of diabetes in NOD mice. *Immunol Today* **11:** 147–149.

Lowis GW (1990). The social epidemiology of multiple sclerosis. *Sci Tot Env* **90:** 63–100.

Milonas I (1994). Epidemiological data of multiple sclerosis in northern Greece. In: *Multiple Sclerosis in Europe. An epidemiological update*. Lauer K, Firnhaber W (eds). Alsbach-Bergstrasse: Leuchtturm-Verlag/ LTV Press, pp 332–333.

Muntoni S, Songini M, Sardinian Collaborative Group for epidemiology of IDDM (1992). High incidence of insulin-dependent diabetes mellitus in Sardinia. *Diabetes Care* **15:** 1317–1322.

Poser CM (1994). Notes on the pathogenesis of multiple sclerosis. *Clin Neurosci* **2:** 258–265.

Poskanzer DC, Sheridan JL, Prenney LB, Walker AM (1980). Multiple sclerosis in the Orkney and Shetland Islands. II. The search for an exogenous aetiology. *J Epidemiol Community Health* **34:** 240–252.

Rosati G (1990). Epidemiologia della sclerosi multipla. In: *Manuale di Neuroepidemiologia Clinica*. Rosati G, Granieri E (eds). La Nuova Italia Scientifica: Roma, pp 143–182.

Sibley WA (1986). Risk factors in multiple sclerosis–implications for pathogenesis. In: *A multidisciplinary approach to myelin diseases*. NATO-ASI series. Serlupi CG (ed). Plenum Press: New York, London, pp 227–232.

Siva A, Radhakrishnan K, Kurland LT, O'Brien PC, Sawnson JW, Rodriguez M (1993). Trauma and multiple sclerosis: a population-based cohort study from Olmsted County, Minnesota. *Neurology* **43:** 1878–1882.

Weinshenker BG, Rodriguez M (1995). Epidemiology of multiple sclerosis. In: *Handbook of Neuroepidemiology*. Gorelick PB, Alter M (eds). Marcel Decker: New York, pp 533–564.

WHO Expanded Program on Immunization (1997). Lack of evidence that Hepatitis B vaccine causes multiple sclerosis. *Weekly Epidemiological Record* **72:** 149–156.

Zilber N, Kahana E (1996). Risk factors for multiple sclerosis: A case-control study in Israel. *Acta Neurol Scand* **94:** 395–403.