Epidemiology of Multiple Sclerosis: A Critical Overview

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ABSTRACT: The decisive conclusions to be drawn from the available epidemiological data, mostly geography and prevalence, of MS are: (1) a north-south (as well as west-east in the United States) gradient exists independent of genetic/racial factors; (2) major differences in prevalence occur in the absence of latitude differences; (3) individuals from the same ethnic derivation have either similar prevalence rates or very different prevalence rates in widely separated geographical areas and (4) specific resistant isolates are shown to exist regardless of latitude. Existing information leads to the almost inescapable conclusion that the epidemiology of MS cannot be explained by any single known environmental or genetic factor(s) in isolation. A combination of a heterogeneous distribution of both genetic and environmental factors appears to be required to explain the available data on MS.

RÉSUMÉ: Épidémiologie de la sclérose en plaques: une revue critique. Les conclusions formelles que l'on peut tirer des données épidemiologiques disponibles qui concernent surtout la géographie et la prévalence de la sclérose en plaques (SEP) sont: 1) il existe un gradient nord-sud (ainsi que ouest-est aux Etats-Unis) indépendant de facteurs génétiques/raciaux; 2) on observe des différences majeures dans la prévalence pour des latitudes identiques; 3) les individus de même origine ethnique ont des taux de prévalence similaires ou tres différents lorsqu'ils résident dans des régions très éloignées les unes des autres; 4) des isolats spécifiques résistants, sans égard à la latitude, one été démontrés. Des données actuelles, on ne peut que conclure que l'epidémiologie de la SEP ne peut être expliquée par un seul ou des facteur(s) environnemental(aux) ou génétique(s) isolé(s). Une combinaison d'une distribution hétérogène de facteurs, tant génétiques qu'environnementaux, semble être nécessaire pour expliquer les données actuelles sur la SEP.

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The non-random geographic distribution of multiple sclerosis (MS) has provided considerable allure for epidemiologic study since the patterns are believed to reflect underlying causes.[1] Such studies have traditionally focussed on the geographic distribution (comparing prevalence data) or on case-control studies, which seek to establish correlations with putative causal environmental factors. There are few, if any, diseases of unknown cause with such detailed information available about worldwide prevalence and incidence. Despite this wealth of data, the results of epidemiological studies have often led to ambiguous interpretation rather than to definitive correlations supporting specific environmental hypotheses. In general, there has been more consensus for demographic and clinical features than for concepts of pathogenesis and for treatment.

Charcot[2] was the first to comment on the geographic distribution of MS by noting that while prevalent in France, the disease was not well-recognized in Germany or England. Subsequent study has shown both these countries now actually surpass France in prevalence and incidence and perhaps always have done so. This epitomizes the importance of a disciplined and uniform epidemiologic approach in studies of disease prevalence.

Key factors for successful epidemiological studies include accurate diagnosis and unbiased case ascertainment, both of which pose special problems in MS. Certain diagnosis (and exclusion of diagnosis) of MS is not always possible in the living patient, even with modern advances in laboratory diagnosis.[3] An obstacle in identifying cases and controls for epidemiological studies is the acknowledged lagtime from the clinical onset of MS to diagnosis, which now averages some four years. Complete case ascertainment in a defined geographic region lessens the chance that observations result from subtle or unrecognized selection bias. Repeat surveys routinely appear to increase prevalence figures. Comparison of prevalence rates is not without hazard since methodology is rarely identical.

In an attempt to explain the geographic distribution of MS, considerable effort has been focussed on traditional environmental factors. There have been numerous supporters for a

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purely environmental causation of MS and the attractiveness of this notion derives from the promise that a relatively simple act of omission (or commission) could serve to prevent the disease. The intensive study of MS prevalence in the 1950's and 1960's coincided with research on paralytic poliomyelitis which culminated in the elucidation of the cause and the subsequent development of an effective vaccine. Not surprisingly, parallels were sought between the epidemiology of the two diseases. Prevailing concepts of the geographic distribution, age specificity of a putative precipitating infection and socioeconomic predilection in MS have owed some of their vitality to analogizing with poliomyelitis.[4]

Contemporaneously, the notion of a common viral infection of long latency in which only a relatively small proportion of those affected by the virus actually develop the disease in question became popularized. A critical age for susceptibility was suggested by migration studies and the identification of "slow viruses" provided both precedent and analogy to support the long latency concept (see below). Extrapolating to the observed north-south gradient in the Northern Hemisphere for MS, it was suggested that children in those parts of the world (regions nearer the equator) with poorer sanitation would be exposed to the "virus" at an earlier age compared with those living in more temperate and developed areas. Younger children could thus develop immunity by the time they reached the critical age for disease susceptibility. Similarly, this hypothesis could explain some, but not all, of the racial differences in MS within a defined geographic area. It cannot be excluded that genes resulting from racial admixture may, to some degree, be responsible for the development of MS. For example, the disease is relatively common in American Blacks compared to African Blacks who have less Caucasian ancestry.[5,6]

Evidence against the age/social stratum-specific latent virus theory has come from Australia where there is a two-fold difference in the prevalence of MS between Perth and Hobart, but sanitary arrangements are comparable[7] and Israel where differences in prevalence could not be explained by sanitation.[8]

The influential studies of migration to South Africa[9] and Israel[10,11] again implicated some crucial childhood event related to the later development of MS. The demonstration that a number of infections of the central nervous system could be followed by a long delayed expression of symptoms and signs (e.g. subacute sclerosing panencephalitis, Kuru) refocussed attention on events of early life. However, the mechanism by which observed epidemiological facts were explained by inferences drawn from these possible analogies has been neither crystallized nor well-defined.

Prevalence and Incidence of Multiple Sclerosis

Overview

In general, accurate incidence rates for MS are difficult to obtain, especially because of uncertainty about the date of disease onset (initial symptoms are often subtle and only recognized in retrospect) and lagtime. In addition, diagnostic uncertainty in early stages is also a factor, as incidence data depend on relatively early cases. For these reasons, the majority of epidemiological studies on MS have either made deductions about incidence from prevalence and/or mortality data or have been limited to prevalence data alone. Kurtzke[12] classified MS prevalence rates into "high", "medium" and "low" risk groups. Rates from 30 per 100,000 population characterize "high risk" areas such as northern Europe, northern United States, Canada, southern Australia and New Zealand. "Medium risk" regions (prevalence between 5 and 25 per 100,000 population) may include southern Europe, southern United States and northern Australia. "Low risk" areas (prevalence less than 5 per 100,000 population) include Asia and perhaps parts of South America. However, even within a general geographic region, there can be considerable variation.[13] The marked difference in prevalence between Sicily and Malta serves as an outstanding example of this variation for two areas in close proximity (see Figure 1).[14,15] Such variation may be explained by environmental factors, genetic factors or a combination of the two.

Prevalence is easier to calculate than incidence since all cases are included, regardless of disease duration. However, accurate assessment of prevalence is still difficult with a major problem being that prevalence data must rely on diagnostic accuracy which, over several decades, has not remained constant. Accurate prevalence rates also depend on the completeness of case ascertainment. It is recognized that the smaller the community being surveyed, the more complete the case-finding. In addition, comparison of prevalence rates between areas must include an assessment of differences in disease diagnosis and case management over the study period. For example, in a less developed area or one with less accessible medical care, diagno-

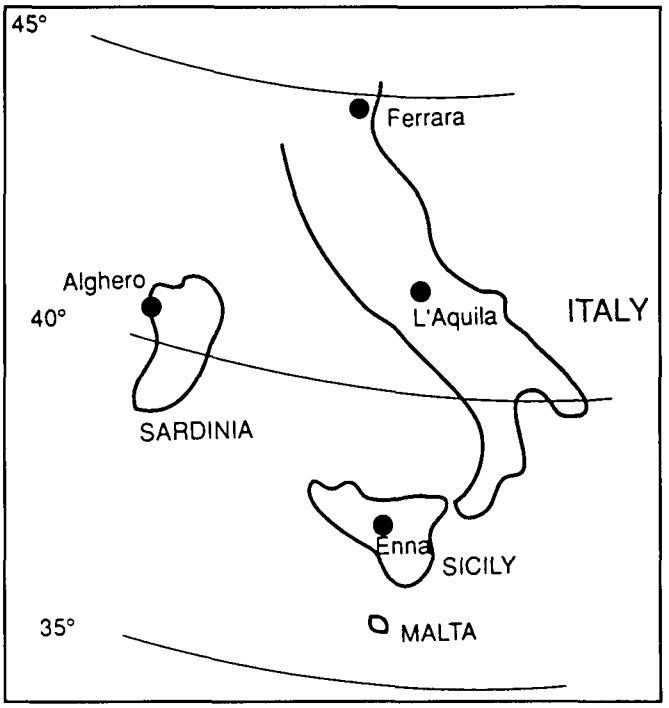

Figure 1: Comparison of Prevalence Rates for Italy, Sardinia and Sicily.

	Prevalence per 10^5	Reference
Alghero, Sardinia	*50.0*	*Rosati et al.*[159]
Enna, Sicily	*53.3*	*Dean et al.*[15]
Malta	*4.2*	*Vassallo et al.*[14]
L'Aquila, Italy	*33.2*	*Salerni et al.*[160]
Ferrara, Italy	*46.1*	*Granieri et al.*[161]

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sis may be less certain and survival diminished. However, this may in reality be an artifact of less frequent diagnosis of earlier and benign cases on one hand and diminished survival among more severe cases on the other. Even within North America, comparisons between Canada and the United States are influenced by differences in health care systems. Since Canadians have essentially equal financial access to diagnostic procedures and medical care, the MS population attending Canadian medical centres may potentially be more representative of the overall MS population for disability distribution (benign/mild to severe) and also for ethnicity and socioeconomic distribution. Given the relative homogeneity of Canadian health care, prevalence comparisons within this country may have more than average validity. Finally, major changes in birth rates over the time period evaluated can influence crude prevalence rates, thus emphasizing the value of age-specific prevalence rates.

Therefore, in reviewing the massive literature on MS prevalence, it is critical to assess the methodology of each study and to only compare data from different regions after carefully determining whether such comparisons are valid. This point and its application are clearly demonstrated in the analyses of prevalence by Kurtzke, who has very well summarized this large body of literature.[12,16]

As early as the 1920's, it was recognized that the distribution of MS was not uniform across geographic regions.[17-20] In general, all types of epidemiological surveys (prevalence, incidence, mortality) find that in temperate climates, many economically-developed occidental countries tend to have a higher rate of MS. In the Northern Hemisphere, a diminishing north-south gradient for MS prevalence has been well-described.[21,22] The reverse, a south-north gradient, has been reported in the Southern Hemisphere.[22,23]

Lessons from Animal Models of Autoimmune Disease

It is beyond the scope of this review to discuss the genetics of spontaneous autoimmune disease in mice. However, all models studied show polygenic inheritance of susceptibility and some demonstrate fascinating epidemiologic lessons. The best understood of these models is the non-obese diabetic inbred mouse (NOD) which, when shipped in colonies around the world, showed a markedly variable penetrance of diabetes, despite documented purity of breeding stocks and genetic homogeneity.[24] Despite the presence of the appropriate background of genetic susceptibility, the penetrance proved to be very strongly influenced by early life diet, cleanliness of environment and viral contamination of breeding colonies. A germ-free environment in early life resulted in full penetrance of diabetes. It is too early to know if these observations are relevant to the epidemiology of MS but they serve to emphasize several relatively unexplored avenues in MS and to provide a fascinating example of the interaction of genes and early life microenvironment. (For more in depth discussion of lessons from animal models, see reference 25.)

Temporal Changes

The epidemiological literature contains numerous examples of changes in incidence and prevalence for specific disorders over time. However, these follow-up studies must be critically assessed to determine whether observed changes are real or reflect changes in medical practice, environment or other factors. In MS, it is generally recognized that more recent surveys and repeat surveys frequently find higher prevalence rates (see Table 1). The literature contains numerous such examples but the reverse has also been reported (e.g. Winnipeg, Manitoba and Western Poland).

Several Canadian prevalence studies have been conducted.[26-34] Re-evaluation of the same population was first done in Winnipeg, Manitoba, the site of the earliest prevalence study in the country. The initial survey, based on data from patient records and death certificates for the years 1939 to 1948, found a prevalence rate of 39.6 per 100,000 population. A follow-up study in 1961[28] diagnostically re-evaluated 144 of the initial study group.[27] Diagnoses remained consistent for 71.5% of cases.[28] Of the 109 patients diagnosed as "probable MS" in the first study, re-evaluation confirmed this diagnosis in 85 cases (78.0%). Of the remaining 24 cases, seven (6.4%) were reclassified as "possible MS" and the rest were diagnosed as either "unlikely MS" (14/109; 12.8%) or "not MS" (3/109; 2.8%). In part because of more rigid diagnoses, the prevalence rate in the follow-up study[28] decreased to 35.4 per 100,000 population – see Table 1. In Western Poland, a resurvey similarly found a lower prevalence rate in the more recent study[35,36] (see Table 1), but a possible explanation was that the findings may reflect an increase in population figures due to a higher birth rate rather than a true fall in MS frequency.

Published prevalence rates in Canada have increased in more recent surveys. This was most dramatically noted in the study from Saskatoon, Saskatchewan which reported a prevalence rate of 134 per 100,000 population.[32] Initial reaction was that research should focus on Saskatoon to determine why the prevalence was so high. However, it soon became clear that this rate was probably more related to the timing of the survey rather than specific risk factors for MS being higher in Saskatoon. At the time of publication, the Saskatoon study was the only one in recent years designed to specifically determine prevalence. Furthermore, improved survival, the availability of various diagnostic tests to assist in the diagnosis of MS,[3] especially in early and benign cases, and the institution of the universal coverage medical insurance program in Canada all contributed to the apparent rise in prevalence. Subsequent studies, including both coasts of Canada and the province of Ontario[26,29,34] also reported comparable prevalence rates (see Figure 2), with the notable exception of Newfoundland where the prevalence was only half that reported in the other Canadian centres.

Incidence and prevalence rates for MS have been repeatedly reassessed for Rochester and Olmsted County, Minnesota, largely because of the excellent data base at the Mayo Clinic. The reported prevalence rate in Rochester increased from approximately 46 per 100,000 in 1915[37] to 108 per 100,000 in 1978[38] and to 173 per 100,000 in 1985[39] – see Table 1. Of interest, the incidence rate for Rochester remained stable at about 3.6 per 100,000 from 1905 to 1974.[37,38] However, re-evaluation of all possible MS cases for the period 1905 to 1984[40] found an increased crude incidence rate of approximately 3.4 and 7.7 per 100,000 population for males and females respectively. It remains uncertain whether this increase in incidence is real or reflects less rigid application of diagnostic criteria and/or improved case ascertainment, study design and diagnostic capabilities.[38] These figures represent the highest incidence or prevalence rates reported in North America. It will be of great interest to know if this incidence will be maintained. Similar findings

are reported from western Norway. In Hordaland County, the incidence for definite/probable MS appears to have increased from 1.12 per 100,000 in 1953 to 1957 to 3.50 per 100,000 for 1973 to 1977.[41] The incidence for 1978 to 1982 was lower than for the previous five year period, but these data must be interpreted with care because of the relatively long interval from MS onset to diagnosis. In Möre and Romsdal County, the average annual incidence increased from 1.94 per 100,000 during the period 1950 to 1954 to 3.78 per 100,000 for 1975 to 1979.[42]

Similar reports of increased prevalence rates over time have been reported in both the Northern and Southern Hemispheres[7,23,43-46] (see Table 1). The question of an apparent increase in MS prevalence has dashed the hopes of those who may have thought that they had heard the last of MS prevalence studies. In fact, the lack of understanding of the nature of the environmental effect demands an open mind. The implications of an increasing prevalence are too important to ignore. Although pathological confirmation of these changes in prevalence rates are elusive, data from high risk areas show that silent MS at autopsy may approach symptomatic MS in prevalence.[47]

Migration Studies

Migration studies, at least in theory, should be decisive in distinguishing between environmental and genetic factors. Studies of migration are much easier in concept than in execution. In principle, studies focus on migrants who move from an area of high risk to an area of low risk or vice versa. If migrants adopt the risk of their new area of residence, an environmental cause is believed to be operative. However, a number of undocumented assumptions are often made in these studies, the most important being that migrants are representative of the country from which they come. Secondly, it is assumed that these migrants, when they settle in their new homeland, distribute themselves randomly. It is doubtful if either of these assumptions is ever true. The greatest migrations in recent history have invariably been prompted by religious persecution, wars or other upheavals. As well, migrants are commonly selected for economic, social, religious, health-related and even personality and anthropologic characteristics. The most striking example in which these considerations were paid no heed may have been the study of Vietnamese migrating to France whose MS risk appeared to increase. These migrants all had a French parent which, as this affected their ability to emigrate from Viet Nam,

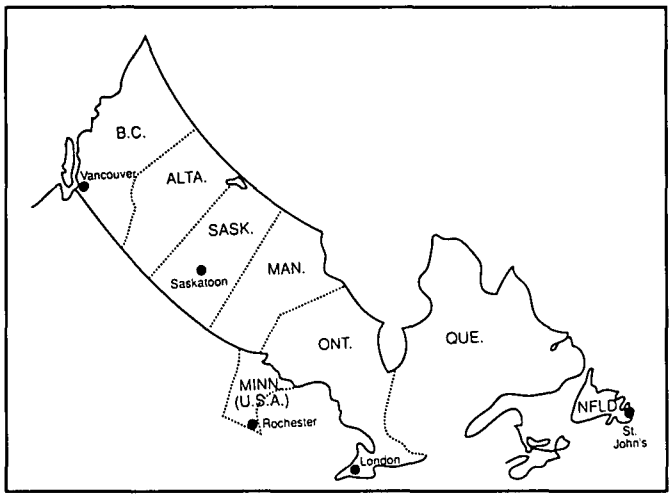

Figure 2: Comparison of Prevalence Rates across Canada and for Rochester, Minnesota.

	Prevalence per 10^5	*Reference*
British Columbia (1982)	*91.0[a]*	*Sweeney et al.[26]*
Saskatoon, Saskatchewan (1977)	*110.0[a]*	*Hader et al.[32]*
London, Ontario (1984)	*94.0[a]*	*Hader et al.[29]*
Newfoundland (1985)	*55.2[a]*	*Pryse-Phillips et al.[34]*
Rochester, Minnesota (1985)	*173.0[a]*	*Wynn et al.[39]*

[a]Prevalence rates include probable MS only. Rates may thus differ from those in Tables 1 and 2 which may include possible cases also.

Table 1: Temporal Changes in the Prevalence of Multiple Sclerosis

Location	Prevalence Date or Period	Prevalence/ 100,000 Population[a]	Reference
I. Canada			
Winnipeg, Manitoba	1939-1948	39.6	Westlund & Kurland[27]
Winnipeg, Manitoba	Jan 1, 1960	35.4	Stazio et al.[28]
II. Rochester, Minnesota			
	1915	46.0	Percy et al.[37]
	1978	108.0	Kranz et al.[38]
	Jan 1, 1985	173.0	Wynn et al.[39]
III. Australia			
Perth	June 30, 1961	19.6	McCall et al.[7]
Perth	June 30, 1981	29.9	Hammond et al.[23]
Newcastle	June 30, 1961	19.3	McCall et al.[7]
Newcastle	June 30, 1981	36.5	Hammond et al.[23]
Hobart	June 30, 1961	33.0	McCall et al.[7]
Hobart	June 30, 1981	75.6	Hammond et al.[23]
IV. Western Norway			
Hordaland County	Jan 1, 1963	20.0	Presthus[45]
	Jan 1, 1983	59.8	Larsen et al.[41]
More & Romsdal County	Jan 1, 1961	24.3	Midgard et al.[42]
	Jan 1, 1985	75.4	Midgard et al.[42]
V. Barbagia, Sardinia			
	Dec 31, 1975	40.7	Granieri and Rosati[43]
	Oct 24, 1981	65.3	Granieri et al.[44]
VI. Western Poland			
	Jan 1, 1965	51.19	Cendrowski et al.[35]
	Dec 31, 1981	42.87	Wender et al.[36]

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was presumably not true of those unable or unwilling to migrate. However, this obvious genetic difference was ignored since the population remaining in Viet Nam was used as the comparison group for the "expected" prevalence of MS among Vietnamese migrants to France.[48]

The frequency of MS differs among populations of the same ethnic origin, some of whom have remained in the region of origin and others who migrated to areas where MS occurs at a different rate from the region of origin. It was first shown in South Africa that immigrants tend to adopt the low MS frequency patterns seen in the indigenous population.[9] This trend has been reported for migration to and from both high and low risk prevalence regions.[9-11,48-50] However, not all of these findings can be accepted unreservedly, as illustrated by the Israeli studies[10,11] which concluded that age at migration was an important risk factor for developing MS. However, these data assume that migrating children and adults are a homogeneous population, yet recent work[51] suggests that this may be incorrect. The prevalence of MS is clearly higher among Ashkenazi (European) Jews than Sephardic (African/Asian) Jews. That these two groups are genetically different is shown by differences in the incidence and prevalence of many known genetic disorders.[52] After World War II, the period used for the Israeli immigration studies, it is likely that there were relatively more Sephardic Jews among migrating children and relatively more Ashkenazi Jews among migrating adults because of the holocaust which tended to spare whole Sephardic families living in Spain, Turkey and Bulgaria (personal communication, Israeli consul, Toronto). On the other hand, a relatively high proportion of Ashkenazi Jews may have migrated as single adults or as partial family units. These considerations may conceivably account in part for the observation that those who immigrated to Israel as children had a lower risk to subsequently develop MS compared to those who immigrated at a later age.

Another weaknesses in migration studies is the relatively small size of the study groups. As well, it is difficult to compare studies done at different times, even in the same geographic region, because the prevalence of MS is steadily rising in most areas due to improved diagnostic techniques and survival.[26,28] For example, few neurologists were in practice at the time of the initial study on immigrants to South Africa[9] and fewer than 20 cases of MS were identified in the most informative groups. A more recent study of children born in the United Kingdom to parents who immigrated from the West Indies found that the prevalence of MS approaches that seen in native Londoners.[50] However, the study was based on a small number of index cases drawn from a population diffused throughout a vast metropolis in which the total number of "at risk" individuals is difficult to define.

In conclusion, results from migration studies are not easily interpreted and are often ambiguous. Genetic and environmental explanations of observed results are not mutually exclusive.

Geographic Clusters

In reviewing epidemiological studies from around the world, there are numerous reports of "clusters" or "hot-spots" where several cases of MS have occurred at a similar point in time, grew up together or were exposed to a specific locale over the same period of time. Examples of reported clusters include Key West (Florida),[53] Henribourg (Saskatchewan),[54] workers in a zinc-related manufacturing plant,[55] Colchester County (Nova Scotia),[56] Vaasa (Finland),[57] Hordaland (Norway),[58] Los Alamos County (New Mexico)[59] and Mansfield (Massachusetts).[60] Analysis of such clusters is less than straightforward since the denominator (the number of groups from which the identified high risk subgroup has been selected) is unknown, but can be anticipated to be large. The highest known prevalence rates for MS are in the Orkney Islands (309 per 100,000 population) and Shetland Islands (184 per 100,000 population).[61] Within the Orkney Islands, clustering of cases in time and space have been reported.[62] Lifetime data showed temporal/spatial clustering of MS patients at least 21 years prior to disease onset and just prior to onset. Each of the two time clusters appeared on three separate islands. No clustering could be demonstrated in the Shetland Islands.

It has not yet been possible to explain clusters. It is, however, important to consider such reports as thoroughly as possible in a continuing attempt to identify causal agents and also to verify the veracity of a reported cluster. For example, a recent report of a cluster in Ohio was found to be erroneous after thorough investigation of reportedly affected individuals.[63]

Epidemics

There have been two MS "epidemics" identified since World War II. The first and most dramatic has been in the Faroe Islands, whose population is derived largely of Scandinavian ancestry. Prior to World War II, there were no reported cases of MS in the Faroe Islands, but 46 cases were identified from 1943 to 1982.[64,65] The point prevalence was reported as 41 in 1950, 64 in 1961, 38 in 1972 and 34 in 1977. These data have been interpreted to indicate a point-source epidemic temporally related to the stationing of approximately 8,000 British troops on the Islands during World War II. However, although the investigations in these studies made impeccable use of available methodology, their interpretation has been open to criticism[66-68] and rebuttal.[69] A major issue yet to be clarified is why British troops have not transmitted MS to many other exposed and previously virgin populations, such as in Africa, or why new cases of MS have ceased to occur in the Faroe Islands.

A second, but less convincing epidemic reportedly occurred in Iceland, also in relation to the stationing of British troops during World War II. The annual average incidence of MS during the period 1945 to 1954 was 3.2 per 100,000 population compared with incidence rates of 1.6 per 100,000 population for 1923 to 1944 and 1.9 per 100,000 population for 1955 to 1974.[70] Kurtzke and colleagues[69] conclude that the incidence of MS during the period 1945 to 1954 meets the criteria for a point-source epidemic whose tail thereafter merges with the baseline for Iceland. However, the situation in Iceland differs from that in the Faroe Islands in that MS did exist prior to the occupation by British troops. As the first neurologist in Iceland only arrived in 1942,[70] this may have influenced the apparent increase in MS over the next few years, particularly among younger Icelanders.

Despite these reported epidemics, the identity of the putative infectious agent(s) remains unknown. Many observers remain unconvinced that these tantalizing data have proven transmissibility. Finally, the action of a transmissible agent is only one possible explanation for the observed findings. It is possible that the introduction of a large number of common viruses into a virgin susceptible population could serve to trigger an apparent epidemic without the implication of a specific transmissible agent.

Sex Ratio

Females are more susceptible to MS by a factor which varies among surveys but approaches 2:1 in population studies.[71] Males have a mean age of onset approximately a year or two later than females and also have a greater tendency for a progressive course from disease onset.[72-74] The female preponderance is even more pronounced (3:1)[75] if MS onset is before age 16. It has been suggested that as these figures are based on prevalence rates, they may reflect differential survival among females and males. However, a recent study on cause of death among patients attending Canadian MS Clinics found that survival did not differ according to sex.[76] It is thus quite likely that factors other than sex-related influences on mortality explain the observed sex ratio in MS. Differences in immune responsiveness may be influenced by neuroendocrine interactions with the immune system. Weitkamp[77] reviewed the literature and found that relatives (siblings, second-degree relatives, first cousins) concordant for MS were more often of the same sex, but this was not confirmed.[78] The observation of Weitkamp[77] does not necessarily imply a genetic/hormonal mechanism among siblings since such pairs may in fact have more environmental sharing compared with unlike-sex siblings.[79] Unlike-sex siblings of MS patients also have a significantly higher risk to develop MS compared with the general population.[9,10]

Age of Onset

Diagnostic criteria[3] now define the age of onset range as 10 to 59 years, extending the upper age limit from age 50.[80] The mean age of onset is from 29 to 33, being slightly younger in females.[77] Several studies have reported that approximately 0.3% of patients have the clinical onset under age 10.[75] Duquette and colleagues[75] reviewed childhood MS (onset before age 16). They found that childhood MS is more frequent among females (75.2%) and often follows a relapsing-remitting course (56%). The initial attack, from which there is usually complete recovery, tends to involve afferent structures of the central nervous system and the progress is usually slow. Conversely, MS may onset after age 59,[81,82] even into the eighth decade. The differential diagnosis is usually less straightforward in older patients who tend to have a chronically progressive course similar to that characteristic of many degenerative diseases seen in older age. For example, older patients could have occlusive cerebrovascular disease which can occasionally produce a stepwise and fluctuating clinical course that can mimic MS.

Recent studies at the MS Clinics in London and Vancouver[83,84] have found a correlation in age of onset among sibling pairs concordant for MS. In addition, a stronger correlation was observed when concordant monozygotic twin pairs were compared with non-twin MS sibling pairs,[83] suggesting that age of onset in MS is partly under genetic control.

Precipitating Factors

There are a number of factors which have been proposed as influencing the onset of symptoms or worsening of MS. These include diet[85] and heavy metals[55,86] as well as trauma, emotional stress, lumbar puncture, surgery and anaesthesia, pregnancy, exertion, fatigue and heat.[87] However, none of these are universal precipitating factors and several are supported only by methodologically weak or unconfirmed studies, often of an anecdotal nature.

Infection

Identification of clusters and epidemics has often been interpreted as support for the role of infectious agents as causal factors in the onset of MS. Canine distemper virus was proposed as a leading candidate in the 1970's,[88] but subsequent case-control studies have failed to support this.[89-91] However, surveys of antibodies to different viruses in various MS populations worldwide have shown that on average, MS patients have high antibody levels to many viruses, measles included. Therefore, existing data give little support to the theory that MS results from exposure to a single, relatively rare virus.

The role of infectious agents in precipitating the clinical onset or relapses of MS remains unresolved. Most research in this area has been based on retrospective data and recall bias becomes a factor. It has been estimated that the onset of MS was preceded by a reported infective disease in about 10% of cases.[87] Sibley and colleagues[92] found that minor respiratory tract infections preceded 27% of MS relapses. Another report[93] found that chronic sinus infection was significantly associated with the timing of MS relapses, as well as with the age and season when these occurred. Sibley and Foley[94] reported a seasonal increase in MS relapses in Ohio during the months when respiratory infections are common. Subsequent work[95] in London, Ontario has confirmed this pattern for disease onset. It is however not clear whether these seasonal influences are related to viral infection or to some other concomitant. Does the same factor(s) influencing seasonal variation also account for some of the geographic gradient? The relationship between infectious agents and MS remains unclear. It is conceivable that infection in general may act as a non-specific trigger for the immune system by initiating the onset of MS or by triggering a relapse.

Trauma and Stress

The role of trauma as a possible precipitating factor in MS was first raised by Charcot[2] who hypothesized an association between MS onset and exposure to cold, falling, illness or stress. Although clinical experience suggests that trauma, physical stress and/or emotional stress may be associated with the onset or relapse of MS, any causal relationship has yet to be clearly and repeatedly demonstrated. In a systematic prospective study of 130 MS patients and 82 age- and sex-matched controls, Bamford and colleagues[96] failed to prove a statistical association between traumatic events and MS relapses, although individual case reports were noted. In reporting MS relapses in relation to trauma, recall bias is always a concern and often the trauma as in a fall has been symptomatic rather than causal.[97]

Pregnancy

The original and classical study on the association between pregnancy, delivery and MS relapses was done by Millar and colleagues[98] who found that the average relapse rate per pregnancy year (nine months gestation plus three months following delivery) was 0.265, elevated compared with the rate of 0.10 relapses per year experienced by women who did not have pregnancies. It is troublesome that neither of these rates approached the 0.5 to 1.4 attack(s) per year found in prospective studies.[99-101] Subsequent retrospective studies continued to confirm the observation that the period following delivery posed the highest

risk for a MS relapse, but that gestation itself was relatively quiescent with respect to disease activity.[87,102] As with other studies on MS, the major methodological problem with research on the relationship between MS and pregnancy has been the use of retrospective data with their inherent recall bias. The definition of an attack has often been imprecise and not clearly separable from non-specific phenomena associated with the post-partum period. The unusually low relapse rates in the paper by Millar and colleagues serve to emphasize this drawback.

Fifty-five women presenting *prior to the onset of pregnancy* at the Vancouver MS Clinic were followed throughout successful pregnancies and for up to six months after delivery.[103] Relapse rates for these women during the study period were compared. "Expected" rates[104] were based on data for matched controls and the women themselves prior to becoming pregnant (self-controls). A gestational effect was only evident during the third trimester when the observed relapse rate was significantly less ($P < 0.05$) than expected. The mean relapse rate for each of the two 3-month periods following delivery did not differ significantly from expected.

Diseases Associated with Multiple Sclerosis

A number of diseases such as systemic lupus erythematosus,[105] myasthenia gravis,[106-108] ankylosing spondylitis,[105,109,110] inflammatory bowel disease[111] and scleroderma[112] have been reported to be associated with MS. However, none of these reports has as yet been confirmed by appropriate and careful population-based surveys. The most that can be said is that MS does not protect individuals from the above conditions nor does it make those other disorders very much more likely to occur.

Every large MS centre can identify cases in which autoimmune diseases occur in MS patients and there is evidence that there are rare families in which there is a genetic predisposition to autoimmune diseases.[113] In Olmsted County, a detailed survey derived relative risks (rr) for 17 autoimmune diseases including rheumatoid arthritis (rr = 1.8) and autoimmune thyroid disease (rr = 3.3) in MS patients compared with controls.[114-116] The only statistically significant result was for autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease). Similar data were collected in London, Ontario for relatives of 194 MS patients and spousal controls. The results were that there was an increased frequency of poliomyelitis and thyroid disease and a mild reduction of cancer in the MS families compared with controls (A. Rudd, G.C. Ebers – unpublished data). This does not appear to represent a promising avenue of exploration. The data serve rather more to underscore the remarkable organ specificity of MS than to support the hypothesis of some general autoimmune diathesis. It is beyond the scope of this review to discuss all but a selected few possible disease associations with MS.

Diabetes Mellitus

The study in Olmsted County, Minnesota reported a relative risk of 2.5 in MS patients for diabetes mellitus,[114] but this was not statistically significant. Warren and Warren[117] reported a higher association of diabetes mellitus in both MS patients and their relatives compared with controls.

Neoplasia

The study in Olmsted County[118] reported a relative risk of 1.4 in MS patients for neoplasia, but this was not statistically significant. Neoplasia in MS has been reported to occur as expected compared with controls by some[28,119] whereas others have found an increased rate. Zimmerman and Netsky[120] reported a 20% incidence of malignant tumours in 50 autopsied cases of MS, including two brain tumours. Others have also reported concurrent MS and primary brain tumours.[120-123] An autopsy series of 120 cases[125] found neither an increase in the rate of neoplasia among MS patients compared with general controls nor any cases with brain tumours. A recent study[76] found that neoplasia was identified as an underlying cause of death significantly less often among MS patients than expected. While it is conceivable that changes in the immune system may "protect" MS patients from neoplasia, a more likely explanation for these data is that neoplasia is less readily diagnosed in MS patients not having autopsies since the symptoms of neoplasia may often be attributed to MS or be less likely to be investigated in disabled patients. In any event, these studies provide important bases for comparison now that cytotoxic agents have achieved relatively widespread usage.

Uveitis

Uveitis in different forms has been reported in association with various infectious and autoimmune diseases including Behçet's disease, toxoplasmosis, ankylosing spondylitis, sarcoidosis, syphilis and MS.[87] Uveitis has been reported in up to five percent of patients in studied series[87] and an even higher rate is found for perivenous sheathing. The main implications here are the associations with infective/autoimmune disorders and the recognition that the uveal tract constitutes an organ which is not myelinated but which participates in the inflammatory process in a substantial proportion of patients.

Summary

Prevalence – Worldwide

In a review of the epidemiology of MS, it is tempting to visually represent the worldwide prevalence of MS in a single, comprehensive map. However, the reader may find such a map more misleading than it is meaningful. Existing prevalence and incidence studies for most countries are not comparable and must be influenced by temporal differences as well as differences in health care systems, neurological expertise and even cultural practices. For these reasons, we chose to list prevalence data alphabetically by country in a table (Table 2) so that it is retrievable for reference with hopefully less of an implication that these studies can be directly compared.

We decided to illustrate some of the consistent, although somewhat contradictory, conclusions drawn from worldwide prevalence studies using contemporaneous data from the most informative comparative studies.

1) Latitude Effect

Several countries exhibiting relative racial homogeneity show a north-south gradient (e.g. Australia, New Zealand); – see Figure 3.

However, there are a number of exceptions to the north-south gradient when regions of different ethnic derivation are included, as shown by the following two examples. The first example is Sicily and Malta which were simultaneously subjected to a prevalence study[14,15] by the same investigator. Figure 1 shows the bottom part of the Italian "boot" and the two islands in the

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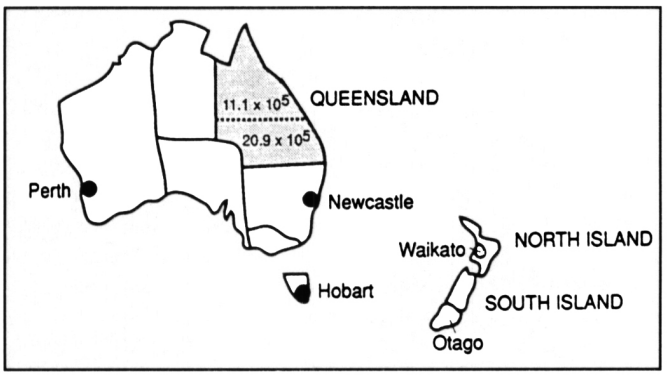

Figure 3: Comparison of Prevalence Rates for Australia and New Zealand.

	Prevalence per 10^5	Reference
Australia		
Queensland	*18.3*	*Hammond et al.*[23]
Perth	*29.9*	*Hammond et al.*[23]
Newcastle	*36.5*	*Hammond et al.*[23]
Hobart	*75.6*	*Hammond et al.*[23]
New Zealand		
North Island, Waikato	*27.9*	*Skegg et al.*[143]
South Island, Otago	*79.4*	*Skegg et al.*[143]

Mediterranean. The second example is in North America where five recent prevalence studies using similar methodology demonstrate an almost four-fold difference in prevalence (see Fig. 2). The rate for Rochester, Minnesota closely approximates rates for Northeast Scotland and the Shetland/Orkney Islands;

2) Individuals from the same ethnic derivation have either the similar prevalence or have very different prevalence rates in widely separated geographical areas.

The former is illustrated by Minnesota and Scandinavia and the latter by the United Kingdom, Northern Australia and South Africa;

3) Specific resistant isolates are shown to exist regardless of latitude.

The sum total distribution of prevalence information for Orientals in North America leads to the almost inescapable conclusion that the geography of MS cannot be explained by any single known environmental factor in isolation. Similarly, it seems very unlikely that the distribution of any genetic factor(s), singly or in combination, could account for the observed world-wide distribution of MS.

Conclusions

It seems appropriate at this point to refrain from any further attempts to force an exclusively genetic or environmental explanation on an abundant collection of facts which simply will not accommodate them. It is timely that any further epidemiological studies be controlled as far as possible for genetic factors and that populations be selected for study in which this possibility is optimized. By doing this, re-examination of a number of individual environmental factors may then prove informative.

Table 2: MS Prevalence: Alphabetical Listing by Country[a,b]

Country	Prevalence Date (Period)	Prevalence/ 100,000 Population[c]	Reference
Australia			
Perth	June 30, 1981	29.9	Hammond et al.[23]
Newcastle	June 30, 1981	36.5	Hammond et al.[23]
Hobart	June 30, 1981	75.6	Hammond et al.[23]
State of Queensland	June 30, 1981	18.3	Hammond et al.[23]
Austria			
Vienna		41.6	Bauer[13]
Upper Austria		29.4	Bauer[13]
Lower Austria		21.7	Bauer[13]
Belgium	1983	80-100	Bauer[13]
Bulgaria		21.2	Bauer[13]
Canada			
Saskatoon, SK	Jan. 1, 1977	134.0	Hader[32]
Newfoundland	March 31, 1985	55.2	Pryse-Phillips[34]
British Columbia	July 1, 1982	117.2	Sweeney et al.[26]
London, Ontario	Jan., 1984	94	Hader et al.[29]
Barrhead, Alberta	Jan. 1, 1990	196	Warren and Warren[126]
Cardston, Alberta		87	Klein et al.[127]
Crowsnest Pass, Alberta		202	Klein et al.[127]
Czechoslovakia (Western)			
Prague		67	Bauer[13]
Northern Bohemia		108	Bauer[13]
Denmark	1965	101	Bauer[13]
Faroe Islands (See section in chapter on "epidemics")			
France			
Brittany	1976-1978	25	Gallou et al.[128]
Chalon-sur-Saone		58	Bauer[13]
Avignon		49	Bauer[13]
Haute Pyrenees		39.6	Bauer[13]
Finland			
Uusima (South)	1979	54	Bauer[13]
Vaasa (West)	1979	91	Bauer[13]
Germany			
Federal Republic	Dec. 31, 1980	68	Bauer[13]
Hesse	Dec. 31, 1980	58.3	Lauer et al.[129]
Democratic Republic			
Rostock		69.1	Bauer[13]
Halle		42.6	Bauer[13]
Greece		10	
Macedonia and Thrace	Dec. 31, 1984	29.5	Milonas et al.[130]
Hong Kong	Dec. 31, 1987	0.88	Yu et al.[131]
Hungary			
Hungarians	Sept. 1949 - Aug. 31, 1981	37	Palffy[132]
Gypsies		2	Palffy[132]
Iceland			
See section in chapter on "epidemics"			
India			
Zoroastrians (Parsis) (Bombay)	March 1, 1988	26	Wadia and Bhatia[133]
Zoroastrians (Parsis) (Poona)	March 1, 1988	58	Wadia and Bhatia[133]
Israel			
Immigrants	Jan. 1, 1966		
Europeans		31.3	Leibowitz et al.[134]

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Table 2: continued

Country	Prevalence Date (Period)	Prevalence/ 100,000 Population[c]	Reference
Israel			
Afro-Asians		6.8	Leibowitz et al.[134]
Native-born Israelis	Jan. 1, 1965		
Europeans		8.8	Leibowitz et al.[134]
Afro-Asians		2.7	Leibowitz et al.[134]
Italy			
Barbagia, Sardinia	Oct 24, 1981	65.3	Granieri et al.[44]
Sicily, Enna	Jan. 1, 1975	53	Dean et al.[15]
Valle d'Aosta	Dec 31, 1985	39	Sironi et al.[135]
Japan		1-4	Kuroiwa et al.[136]
Korea			
Busan	1971-1981	1.8	Kim and Kim[137]
Seoul	1958-1966	2.4	Park[138]
Kuwait	1981-1983	8.3	Al-Din[139]
Libya	July 1, 1984	5.9	Radhakrishnan et al.[140]
Luxembourg	No formal survey		Bauer[13]
Malaysia	1968-1986	2	Tan[141]
Malta		4	Vassallo et al.[14]
Mexico			
(Government workers and their families)		1.5	Alter[142]
New Zealand			
Waikato (North Island)	1981	27.9	Skegg et al.[143]
Otago and Southland (South Island)	1981	79.4	Skegg et al.[143]
Norway			
Hordaland County	Jan 1, 1983	59.8	Larsen et al.[41]
Möre & Romsdal County	Jan 1, 1985	75.4	Midgard et al.[42]
Poland (Western)	Dec 31, 1981	42.87	Wender et al.[36]
Portugal		15	Bauer[13]
Romania			
Brasov, Transylvania		46	Bauer[13]
Cluj, Transylvania		43	Bauer[13]
Bucharest		79.4	Bauer[13]
Danube (Southern Regions)		< 6	Bauer[13]
Saudi Arabia	Jan. 1983 - Dec. 1986	8	Yaquib and Daif[144]
South Africa			
White South Africans			
(English-speaking)	1960	12.7	Dean[9]
(Africaans-speaking)	1960	3.6	Dean[9]
Spain			
Lanzarote (Canary Islands)	Dec. 21, 1987	15	Garcia et al.[46]
Malaga	June 30, 1984	10.9	Bauer[13]
Sweden		130	Bauer[13]
Switzerland		51.4	Georgi et al.[145]
Basel		106	Georgi et al.[145]
Bern		55	Georgi et al.[145]

Table 2: continued

Country	Prevalence Date (Period)	Prevalence/ 100,000 Population[c]	Reference
Switzerland			
Valais		25	Bartschi-Rochaix[146]
Taiwan	May, 1975	0.95	Hung et al.[147]
Tunis		10	Ben Hamida[148]
United Kingdom			
England			
London, Borough of Sutton	Jan. 1, 1985	115	Williams & McKeran[149]
Wales			
South-East Wales (South Glamorgan	Jan. 1, 1985	117	Swingler & Compston[150]
Scotland			
North-East Scotland (Grampian Region)	Dec. 1, 1980	144	Phadke & Downie[151]
Shetland Islands	April 30,1984	170	Cook et al.[152]
Orkney Islands	Sept. 21, 1983	224	Cook et al.[153]
Outer Hebrides	July 1, 1979	97.3	Dean et al.[154]
United States			
Hawaii			
"Orientals"	Jan. 1, 1969	8.8	Alter et al.[155]
"Caucasians"	Jan. 1, 1969	10.5	Alter et al.[155]
California			
Los Angeles (Whites, Los Angeles-born)	April 1, 1970	22	Visscher et al.[157]
Washington (Whites born in King-Pierce Counties)	April 1, 1970	69	Visscher et al.[157]
Minnesota, Rochester	Jan. 1, 1985	173	Wynn et al.[39]
USSR			
Moscow (based on incomplete survey)	1973	32	Bauer[13]

Consensus at the International Federation of Multiple Sclerosis Societies, Hamburg, 1985 is that the prevalence rates for MS in the USSR probably parallel those in the corresponding latitudes of western Europe (Bauer[13])

Yugoslavia			
Croatia	June 30, 1986	143.5	Sepcic et al.[158]

[a]The reader is referred to the appropriate references. These rates are not necessarily comparable with each other, but should provide the most up-to-date information known for the country. Studies vary on the diagnostic criteria, ascertainment and year of study.

[b]This is not meant to be a comprehensive list of *every* prevalence survey ever conducted in a given country.

[c]Age-specific prevalence rates given, when available. Studies vary on the diagnostic criteria for inclusion in the prevalence rate.

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