EPIDEMIOLOGICAL FINDINGS INDICATING AN EXOGENOUS CAUSE OF MS

JOHN F. KURTZKE

Departments of Neurology and Community Medicine, Georgetown University School of Medicine, and Neurology Service, VA Medical Center, Washington, D.C. 20422 (USA)

SUMMARY

The epidemiologic evidence is strong that multiple sclerosis (MS) is an acquired, environmental disease to which whites are especially prone. The evidence is good that the disease is ordinarily acquired long before the onset of symptoms, perhaps near puberty for natives of high risk regions. Migration between risk areas well before onset seems to alter the risk to one intermediate between that typical of the new and the old home lands, regardless whether the move is from low to high or high to low regions. This is best explained by what is called the "prevalence" or the "simple" hypothesis - that the cause of MS will be found where the disease is common. The most recent evidence from two epidemics in the Faroes and in Iceland would further suggest that the disorder is transmittable. If our guess is correct as to its transmission by the military during World War II, we would then have to assume that it is transmittable during the preclinical or latent phase, and further that in that phase it is a far more common entity than the frequency of clinical disease would suggest. The simplest explanation as to the cause of MS would seem to be that of a virus, which however is yet to be identified.

GEOGRAPHIC DISTRIBUTION OF MS IN EUROPE.

Prevalence studies provide our best information on the frequency of disease. However, they are expensive in time, people and money. Despite this, there are now nearly 200 such surveys for multiple sclerosis (MS). Almost all of them have been performed since World War II. Recently I tried to collect these studies and to rate them as well as to quality (1). When the MS prevalence rates are correlated with geographic latitude, we find that in Western Europe the disease is distributed according to latitude within two clusters: a high frequency zone with prevalence rates over 30 per 100,000 population, and a medium frequency zone with prevalence of 5 to 25. The southern division between the high and medium zones extends from the eastern Pyrenees Mountains in an arc through the middle of Switzerland, or from 43° to 47° north latitude. The northern division is at about 65° north. No European area is low, by which I mean prevalence less than 5 per 100,000. Later studies from Ireland, Scotland, the Shetland-Orkneys, lower Saxony, Wallis in Switzerland, and several regions in Italy confirm this pattern (2).

In eastern Europe the distribution is similar, although there were then relatively few good quality studies. More recent surveys of Bucharest, Romania, and of the northwestern corner of Yugoslavia gave prevalence rates of 41 and 32 respectively (3,4). The high-medium dividing line thus extends from mid-Switzerland to the head of the Adriatic Sea at about 44° north latitude and then eastward to the Black Sea.

MS foci. Within western Europe there have also been a number of nationwide prevalence studies. In Denmark, MS is concentrated in the middle and the eastern portion of the peninsula of Jutland, and this focus extends to include the contiguous island of Funen to the southeast. In Switzerland, the disease is concentrated in the northwestern part of the country. Sweden shows two foci, one covering the southern inland lake region from east to west, and a separate one on the coast toward the north- east at 64° - 65° . In Norway the disease is concentrated from the waist from near 64° downward to the coast on the south and east. Overall, there is a sixfold difference in prevalence rates between the highest and the lowest regions in these lands, A difference that seems of biologic as well as statistical significance. It is this clustering that permits the inference that MS is intrinsically dependent on geography, and that it may then be considered an exogenous, environmental disease (5). This same clustering persists when distributions

within small administrative units are assessed as well as those in the large counties (6), and it is not related to the distributions of physicians, specialists or hospitals (7),

Not only is there clustering in these lands, the foci are stable over time. Surveys covering different generations of patients in Denmark are essentially identical. Similar too are such works from Switzerland, and the same holds true for Norway. Prevalence rates by county for old vs new surveys are highly correlated in each of these lands, with a correlation coefficient of about 0.8 (8).

If the disease is stable over time in these lands, we might then see if surveys of contiguous countries provide evidence of any broader geographic patterning. And such is the case. In the north we can define a Fennoscandian focus of high frequency MS (Figure 1). This region extends from the waist of Norway southward, then across southern Sweden and to southwestern Finland, to return across the Bay of Bothnia to Sweden near Umeå at about 64° north latitude (8). Note that Finland, where MS is concentrated in the southwest, serves to bring together the two discrete Swedish foci (6).

GEOGRAPHIC DISTRIBUTION OF MS OUTSIDE EUROPE.

On the other side of the Atlantic, prevalence surveys from the Americas give us all three risk zones. The rates for the northern United States and southern Canada are similar to the high frequency rates of western Europe. Southern US is medium. Both to the north and the south of these areas, the disease is rare (1).

However, we can now provide much more detail for the distribution within the US. We have been studying a series of some 5300 cases of MS among military veterans of World War II or the Korean Conflict. Their disease became manifest during or within seven years after military service. We then matched these cases with their military peers to give us an unbiased, pre-illness case control series of unprecedented size. For white males their residence at entry into service or at birth shows a strong north-south gradient. When the country is divided into three horizontal tiers, the case control ratio is 1.41 in the northern tier of states, 1.02 in the middle tier, and .58 in the southern tier (9).

Figure 1. Distribution of MS in Fennoscandia. Solid areas are significantly above the respective national rates ($X^2_a > 4.0$); cross-hatched areas are high with dubious significance (X^2_a 2.0-4.0); and diagonal-lined areas are insignificantly high ($X^2_a < 2.0$). Open areas are below the national rates. Area boundaries are omitted. Distributions are within 104 areas of Norway, 106 of Sweden, 21 of Finland, and 23 of Denmark. From Kurtzke, 1974 (8).

Returning to the international studies, Australia and New Zealand comprise principally a high frequency zone for 44° to 34° south latitude, and a medium frequency region for 33° to 15° south. Rates from Asia and the Pacific in the northern hemisphere are all low, except that Hawaii is likely to be in the medium zone. Even with later data, there is so far no site in Asia shown to have more than a low prevalence rate for MS. In the southern hemisphere, all rates from Asia and Africa are also low, except for English-speaking native-born whites of South Africa whose rate of 11 is within the medium range. Afrikaans-speaking native whites have the low prevalence rate of 3, while blacks and Coloured have rates of 0 (1,2).

In summation, we may consider the world-wide distribution of MS as comprising three zones of frequency or risk. The high risk zone includes northern Europe, the northern US and southern Canada, New Zealand, and southern Australia. These regions are bounded by areas of medium frequency. Asia, Latin America, and almost all of Africa are of low frequency. South America and much of Africa, though, remain largely unexplored (Figure 2).

RACE AND MS.

Note that all the high risk areas and the medium risk areas have predominantly white populations. Thus MS can be considered the white man's burden. Regardless of residence in the US, in our veteran series, blacks or Negroes have only half the risk of MS as do white males, but they still demonstrate the same marked north-south gradient in risk. With small numbers, this same series suggests a paucity as well for American Indians and for Orientals. Detels et al in California have documented a low prevalence among Japanese-Americans (10). In our series there was an apparent deficit among Spanish-Americans, but this seemed more a reflection of geography than race. Among foreign-born service men from Latin America there was, in fact, an equal deficit for whites and for "other" races (9).

MIGRATION AND MS.

The fate of migrants among these regions of differing risk is vital to our understanding of this disease. Overall, immigrants tend to retain much of the MS risk of their birthplace (Table 1).

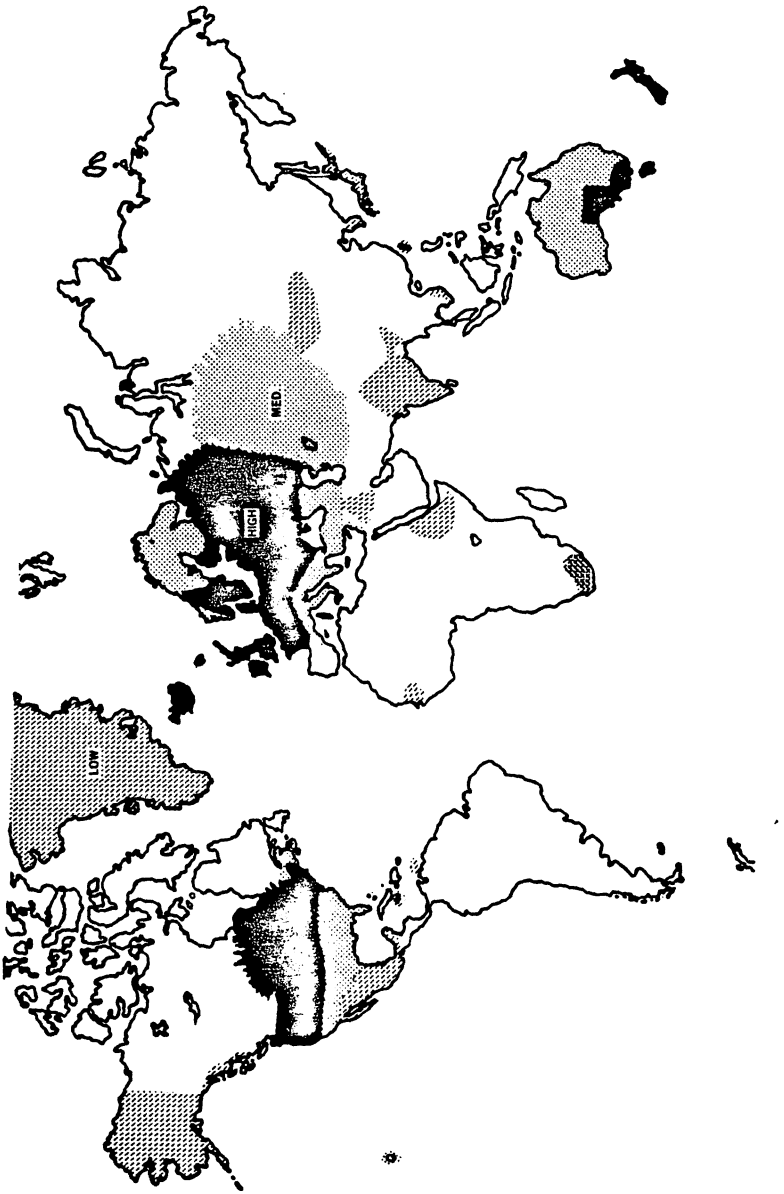

Figure 2. Worldwide distribution of MS within high (solid), medium (dotted), and low (diagonal-dashed) risk areas as of 1974. Open areas are unstudied. From Kurtzke, in press (2).

Table 1. Prevalence Rates per 100,000 Population for Probable Multiple Sclerosis among Native-born and Immigrants. From Kurtzke, 1977 (11)

Immigration site according to its MS risk		Prevalence Rates among Native born	Immigrants from risk areas High	Medium	Low
	High				
(1)	So. Australia	38	37	4	...
	Medium				
(2)	Perth, W. Aust.	40[b]	87[b]	...	...
(3)	Perth, W. Aust.	14	22	...	...
(4)	W. Australia	10	31	...	...
(5)	Queensland	9	15	...	...
(6)	Israel[a]	9[c]	----19[c]----		6[c]
(7)	Israel	4	33	8	3
	Low				
(8)	South Africa	6	48	15	...
(9)	Neth. Antilles	3	59	...	...
(10)	Hawaii[a]	5	----35-----		...

[a] may include "possible" MS
[b] age-specific rate, 40-49 years
[c] age-adjusted to 1960 US population

The evidence for this is primarily for immigrants from high risk areas to low. In South Africa, while native-born whites have an overall prevalence of 6 per 100,000, immigrants from high-risk Europe have a rate of 48 and those from medium-risk Europe a rate of 15. In the Netherlands Antilles, immigrants from the high zone have a rate of 59 as contrasted with the native rate of 3 (11).

Data on low to high areas are sparse. We found three instances of exacerbating-remitting MS among a series of some 3400 half-Vietnamese, who came to France under the age of 20. The cumulative risk of MS was 89 per 100,000. The age-specific prevalence rate was 169 per 100,000 age 20 to 29. Both measures are similar to those for Denmark, but their confidence intervals are wide. Lower confidence limits, though, are far beyond the rates expected for Vietnamese in Vietnam (12).

As stated above, for our veteran series we divided the country into three horizontal tiers of states: a northern tier above 41° to 42° north latitude; a middle tier; and a southern tier below 37° including California from Fresno south. Migrants would be those born in one tier who entered service from another. The case control ratios decline from north to south, for birthplace and for residence at service entry. Those for whom these residences are the same provide the ratios of 1.41 north, 1.04 middle, and .56 south. As to the migrants, those born north and entering service from the middle tier have a ratio of 1.26; if they enter from the south their ratio is .70, only half that of the nonmigrants. Birth in the middle tier is marked by an increase in the MS/C ratio for northern entrants to 1.30, and a decrease to .72 for the southern ones (Table 2). Migration after birth in the south seems to raise the ratios to .62 (middle) and .73 (north). The migrant risk ratios are intermediate between those characteristic of their birthplace and their residence at entry (13).

Table 2. MS/control ratios for white males of World War II* by tier of residence at birth and at entry into active duty (EAD): US only. From Kurtzke et al, 1979 (13)

Birth tier	EAD tier			Birth Total
	North	Middle	South	
		(MS/C ratio)		
North	1.41	1.26	.70	1.38
Middle	1.30	1.04	.72	1.04
South	.73	.62	.56	.57
EAD Total	1.39	1.04	.58	1.04
		(case/control)		
North	1611/1140	112/89	32/46	1755/1275
Middle	125/96	1544/1482	68/94	1737/1672
South	16/22	42/68	439/788	497/878
EAD Total	1752/1258	1698/1639	539/928	3989/3825

*includes those who also served in Korean Conflict

Residence at birth has about the same gradient of risk as does residence at service entry - and therefore about age 24 for WW II veterans. Inferences from these findings as to the likely age of acquisition of MS are twofold: If the disease is acquired over a short interval, then the point midway between birth and 24 would seem most likely. However, the findings are equally compatible with the idea that prolonged or repeated exposure to the presumed pathogen is necessary, and that what we are seeing here is a dose-response curve to duration of exposure.

The best data supporting age 15 as critical for high to low migrants come from the study of European immigrants to South Africa. Their MS prevalence rates, according to age at immigration and adjusted to a population of all ages, show that for immigration under age 15, there is the same medium prevalence rate (13 per 100,000) as for the native-born English-speaking South Africans. But for all older age groups, the prevalence is about 40 to 80, what one would expect from their high risk homelands (14).

EPIDEMICS OF MS.

Thus far, the evidence has been that MS is an acquired exogenous disease with acquisition well before onset, and with a change in the MS risk by migration before onset to different risk areas. There has been no hint that the areas themselves have altered their MS frequencies over time, and certainly no reason to suspect the existence of epidemics of MS. However, our recent experiences suggest otherwise.

Faroe Islands. The Faroes are a group of small islands lying between Norway and Iceland at 62° north latitude and 7° west longitude. Population is some 42,000 for this semi-independent unit of the Kingdom of Denmark, which, until 1948, was a standard county or amt of Denmark proper. In 1972 Hyllested and I began an intensive search for all instances of MS that had occurred on the Faroes. By July, 1977, we had identified 25 cases among native-born resident Faroese, and full details of the study were recently published (15). Among these cases the sex ratio was equal and average age of onset was 26 years. Clinically, only three cases were progressive from onset. Neurologic findings at examination were in accord with other series.

However, point prevalence rates varied markedly over time; and there were no patients with MS in 1939 (Table 3). Mean durations of illness for the living cases at prevalence day were 4 years in 1950, 10 years in 1961, 20 years in 1972, and 25 years in 1977. All but one case began between 1943 and 1960. These 24 cases then meet all criteria for a point-source epidemic.

Table 3. MS on the Faroes: Some characteristics of the MS series, accepted cases, as of various prevalence days. From Kurtzke & Hyllested, 1979 (15)

	Prevalence Day[a]				
Characteristic	1939	1950	1961	1972	1977
Number of cases	0	13	22	15	14
(number of males)	-	(7)	(12)	(6)	(6)
Prev. rate per 100,000	-	40.9	63.6	38.3	33.7
Mean Age @ P.D.	-	30.85-	35.73	42.67	48.43
Mean Age @ Onset	-	26.85-	25.32	23.07	23.71
Mean Duration (yrs.)	-	4.00	10.41	19.60	24.72
Time of Onset:					
Mean	-	7/46	11/50	11/52	9/52
Median	-	1946	1949	1951	1951

[a] Jul 1

The major unusual event that we could discover so far on the Faroes was their occupation by British forces for five years in World War II. There were said to have been 8000 troops on the Islands, or almost one Briton for every three Faroese.

The World War II residences of the MS patients were locales where the British were stationed in 21 of 24 instances. The other three patients also had direct contact with the British. On the other hand, residence at birth for the MS cases did not match the occupation sites nearly as well.

Iceland. With the late Kjartan Gudmundsson, we have since 1974 also been looking at MS in Iceland, a country which shares its history, geography, culture and peoples with the Faroes. With Sverrir Bergmann we are now updating this series beyond 1976 (16).

By year of onset, there appear to be three distinct phases in the history of MS in Iceland: a low and sporadic occurrence early in the century; a sudden rise in 1923 and then a plateau to 1944; then another sudden rise and an irregular plateau thereafter. The annual incidence rates reveal more clearly that there does indeed seem to have been at least one epidemic of MS in Iceland, beginning in 1945. The average annual incidence rate from 1923 to 1944 was 1.6 per 100,000 population. For 1945 to 1954 it was twice as high, at 3.2, and for 1955 to 1964 it was 1.9. With our update, the average annual rate for 1965 to 1974 will be 1.7 per 100,000.

Iceland, too, was heavily occupied during World War II, not only by the British, but also by the Canadians and the Americans. It may well be, then, that in Iceland MS was reintroduced in a fashion similar to the Faroes, and that answers to both the Icelandic saga and the Faroese saga may provide the essential clues to finally deciphering this enigmatic disease which we call MS.

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