The Epidemiological Structure of Multiple Sclerosis in California

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Abstract

A disproportionate number of California multiple sclerosis patients were found to be of Northern European ethnicity. Severity of the disorder was associated with present age, male gender, age at diagnosis, and years since diagnosis. Age at diagnosis was associated with present age, Northern European ethnicity, greater geographical latitude at the time of birth and at the time of diagnosis, and number of years since diagnosis. In contrast to findings in Denmark and Sweden, the present study did not find a disproportionate number of multiple sclerosis patients to have been born in spring and summer months. An incidental and unexpected finding was that about seven percent of multiple sclerosis patients were found to be at least part Native-American, an ethnicity previously regarded to have a very low prevalence of multiple sclerosis.

The Epidemiological Structure of Multiple Sclerosis in California

Prevalence rates for MS have been researched now in well over 250 surveys, almost all conducted post World War II.[1-5] These studies support the view that there is an uneven geographical distribution in the frequency of MS throughout the world with a suggestive north-south gradient (reversed in the Southern Hemisphere) allowing division of the world into low, middle, and high risk zones of prevalence. The Caucasians of Northern and Central Europe are generally more susceptible to multiple sclerosis than populations elsewhere. Extremely high prevalence zones have been found in the British Isles. Poskanzer, Prenney, Sheridan and Kondy[6] found a prevalence of MS of 258 per 100,000 on the Orkney Islands and 184 per 100,000 on Shetland. North-east Scotland has also one of the highest prevalence figures ever registered, 144 per 100,000.[7] The world comprises three zones of frequency or risk. The high-risk zones includes northern and central Europe into the former U.S.S.R., northern U.S.A., southern Canada, New Zealand, and south-eastern Australia.[8] Areas of medium risk consist of southern U.S.A., south-western Norway and northernmost Scandinavia, Siberia, Ukraine and the former U.S.S.R. beyond the Ural Mountains. Except for small aberrant studies in Italy with reported high rates, the entire Mediterranean Basin from Spain to Israel are also of medium prevalence as is most of Australia, possibly Hawaii, the mid-portion of South America and a subset of the Caucasian population of South America and a subset of the Caucasian population of South Africa.[1,8] The low frequency zones encompasses all other known areas of Asia and Africa, Alaska, Greenland, and the Caribbean region, including Mexico and northern South America.[8,9] As to the distribution of MS in the United States, there have been a modest number of prevalence studies.[3] found an average incidence and prevalence of 3 and 35 per 100,000 respectively in persons living south of 37 degrees latitude as compared with 5 and 69 per 100,000 north of 37 degrees latitude. Vermont, Washington and Minnesota have the highest rates of multiple sclerosis of the 50 contiguous of the United States.[8] These states are not only bordering Canada, but have the very high rates of Scandinavian, Anglo-Saxons and other northern European populations, often referred to as the "North Sea people." This possibly explains why the rates of MS in North America, with its predominantly North Sea population, are significantly higher than those in Europe at similar

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latitudes, with predominantly people of Mediterranean origin.[10]

The zone of origin of migrants who then move into geographical regions differing in rates for multiple sclerosis is critical to the understanding of the geographical distribution of this disease. Prior research has demonstrated that immigrants tend to retain much of the MS risk of their birthplace. Migrants moving from high into low-risk areas after the age of 15 years tended to retain the MS risk of their birthplace. Those migrating before the age of 15, however, acquire the lower risk of their new residence.[2,9]

In general, Blacks, Orientals and Hispanics in the United States have much lower rates of multiple sclerosis than Whites in the same geographic residence. On the other hand, prevalence of MS in all three racial groups tends to increase in frequency with increasing geographical latitude. The demographic variable that provides the clearest perspective is gender, with females being at 2 or 3 times the risk than males. At the time of Kurtzke's earlier reviews, the familial concordance rate of MS was demonstrated at between 2 and 17%, with a mode of circa 6%. The concordance among sibs was 1%, 200 per 100,000, and for parents, half of that. Today, we still lack good data on the occurrence of the disease in the children of patients with MS, and reliable data on twins has been sparse and inconclusive.[11] Bobowick, Kurtze, Brody, Hrubec and Gillespie[12] found that one of six pairs of monozygotic twins and none of the eight dizygotic pairs were definitely concordant. These and other data that support low rates of concordance suggest that familial aggregations may be due in part to exposure. Templer, Regier and Corgiat[13] found that the ten states with the highest schizophrenia rates in the United States also had significantly higher multiple sclerosis rates. Additionally, a very high correlation between schizophrenia and multiple sclerosis was found for the six continents.[14,15] Templer, Trent, Spencer, Trent, Mortensen and Gorton[16] hypothesized a similar seasonality of birth distribution for MS as for schizophrenia due to congruence of geographical prevalence and incidence. Although this similarity was not found, a very clear pattern consisting of a seasonal excess of MS births in Denmark was found in the four consecutive months of March, April, May and June. Seasonal fluctuations of birth for individuals with MS in Sweden, also confirms that multiple sclerosis patients tend to have been born in the spring and early summer.[17]

The present study has four purposes: (1) to determine the seasonality of birth of California multiple sclerosis patients; (2) to determine their ethnic distribution; (3) to determine the correlates of symptom severity; and (4) to determine the interrelationships of epidemiological variables using multivariate analysis. The previous epidemiological literature has used either univariate analysis or no statistical analysis at all.

Method

The questionnaire employed is contained in **Table 1** (p.137) The nine items in this questionnaire request personal information about: gender; year and month of birth; eye-color; place of birth; geographic migration and age of migration; ethnicity; familial history of multiple sclerosis; and severity of symptoms according to an ambulation index (ability to walk). The Board of Directors of the Central and Southern California Chapters of the Multiple Sclerosis Society gave permission to contact the members of this society. All of the members of the Central and Southern California Multiple Sclerosis Society were mailed the questionnaire and a letter requesting that they complete the questionnaire. The returned envelopes were opened by employees of the Multiple Sclerosis Society who separated the consent form from the questionnaire. Three thousand and one

Table 1. Questionnaire administered to all subjects.

1. Male ☐ Female ☐

2. Please state MONTH and YEAR of birth:

3. Eye Color: Light Blue ☐ Blue ☐ Blue-Green ☐ Hazel ☐
   Light Brown ☐ Brown ☐ Dark Brown ☐ Other _____

4. Place of Birth _____ Country:_____ State _____

5. How old were you, if/when, you first moved away from your place of birth?
   Age: Name the area that you moved to: _____

6. In what country or state were you first diagnosed with MS? Country/State:
   Your age at that time? _____

7. Please indicate your specific ethnicity or "roots." You may show this by using percentage, for example 50% Irish and 50% German, etc:
   Ethnicity: _____ % _____ %

8. Has anyone in your family, immediate or distant, been diagnosed with multiple sclerosis? Yes ☐ No ☐

9. Please indicate the present disease stage of your medical condition, as closely as possible, according to the levels of severity listed below.

Please check only ONE even though it may not meet your exact condition:

____Diagnosed with M.S. but asymptomatic; fully active.

____Walks normally but gets easily fatigued which interferes with demanding and athletic activities.

____Abnormal gait if episodic imbalance but walks independently.

____Requires unilateral support (cane or single crutch) to walk.

____Requires bilateral support (canes, crutches or walker).

____Use bilateral support and wheelchair on occasion.

____Use wheelchair for most activities.

____Restricted to wheelchair but able to transfer self independently.

____Restricted to wheelchair; unable to transfer self independently.

hundred eighty seven letters were sent to members of the Orange County Multiple Sclerosis Society in Irvine and members of the Fresno County Chapter Multiple Sclerosis Society. Seven hundred fifty three questionnaires were returned by mail giving a 24% return rate. Twenty six questionnaires were discarded because of excessive missing data, or illegibility. Five hundred thirty one respondents were members of the Irvine Chapter of the Multiple Sclerosis Society in Orange County, California and 196 respondents were members of the Fresno Chapter in Fresno County, California. One hundred seventy seven respondents were males (24%) ranging in age from 22 years to 85 years (mean age = 51.02 years). Five hundred fifty subjects were female (76%) ranging in age from 22 years to 85 years (mean age = 50.21 years). One hundred sixty one (22%) respondents (37 males and 124 females) reported that at least one other family member (immediate or distant) had been diagnosed with MS.

Eye color was scored on a continuum from 1 (light blue) eye color to 7 (dark brown/black) eye color after Galton's model of polygenic inheritance classification table as reported by McKusick,(1990). Thirty-nine (5%) of subjects had light blue eyes, 161 (22%) blue eyes, 91 (12%) blue green eyes, 196 (27%) hazel eyes, 26 (4%) light brown eyes, 181 (25%) brown eyes, and 33 (5%) dark brown/black eyes. Eye color was divided into a 1 (light color) category and 2 (dark color) category. Thus Galton's eye color categories were collapsed into two categories, i.e., Galton 1,2,3,4= cat.1 and 5,6,7= cat.2. In terms of ethnicity, a "risk score" was assigned for each subject. This "risk score" identified each subject's familial ethnic origin, as reported by the subject's response in the questionnaire. A score of 3 was assigned to subjects with a high MS risk ethnic background; a score of 2 for medium MS risk ethnic background; and a score of 1 for low MS risk ethnic background.

The risk score for subjects with multiple ethnic backgrounds was generated by weighing each ethnic risk by the percent of that ethnicity as reported by the subject. For example, a respondent who reported an

Table 2. Distribution of United States general population births and MS births for Fresno and Orange counties and expected MS births 1933 through 1962 (except 1940).

	General population		MS subjects	
Month	**N**	**%**	**N**	**%**
January	8,235,739	8.49	56	61.72
February	9,364,425	9.65	63	70.16
March	7,915,045	8.16	49	59.32
April	6,664,257	6.87	63	49.94
May	7,560,358	7.78	43	56.56
June	7,657,065	7.89	66	57.36
July	8,402,961	8.66	60	62.96
August	8,712,331	8.98	66	65.28
September	8,400,344	8.66	62	62.96
October	8,277,146	8.53	62	62.01
November	7,806,860	8.05	73	58.52
December	8,026,674	8.27	64	60.12
TOTAL	97,023,205	100.00	727	727.00

ethnic background of 50% German (3), 25% Spanish (2), and 25% Italian (1) was assigned a risk score of .50(3) + .25(2) + .25(1) = 2.25. For the purpose of comparison of the ethnic distribution of the multiple sclerosis patients to that of general population Californians, the same ethnic categories of 3 (high) 2 (medium) and 1 (low) were used in the correlational analysis. Categories 1 and 2, however, were combined because of the much lower numbers and were referred to collectively as the lower risk ethnic group. According to U.S. government publication (United States Summary, Population Characteristics, 1995), there were 18,674,909 (62.26%) Californians in the higher risk group and 11,317,970 (37.24%) Californians in the lower risk group. Severity of the disease was evaluated as a reflection of degree of ambulation reported by the respondent at the time he/she completed the questionnaire.

The ambulation scale ranged from one (diagnosed with MS but asymptomatic) to nine (restricted to wheelchair and unable to transfer self independently). The mean value of disease stage (as measured by ambulation) was 4.31, (SD = 2.58). The mean disease stage for males was 2.56, (SD = .63) and 2.67 for females (SD = .61). The distribution of general population births for the United States for the years 1932 through 1962 (excluding 1940) was provided by the Public Health Service (Natality Branch). This data was the basis for calculating the expected number of MS births based on proportions of general population births.

Results

Table 2 (p. 138) displays the number of births in each of the 12 months for the present MS patients and the number expected on the basis of the U.S. general population births, $x2$ (11, N = 727) = 15.82, N.S. In dichotomizing the births as in the Templer et al (1992) study with MS patient births in Denmark, 221 (223.22 expected) births were in March, April, May, or June and 506 (503.78 expected) were in the other eight months, $x2$ (1, N = 727) = .03, N.S. In dichotomizing the births as in the Wiberg and Templer (1994) article with combined Denmark and Swedish MS births, 281 (286.18 expected) were in March, April, May, June, or July and 446 (440.82 expected) in the other seven months, $x2$ (1, N = 727) =.15, N.S. There were 607 (83.49%) MS patients in the higher risk ethnic group and 120 (17.51%) MS patients in the lower risk ethnic group. The numbers expected on the basis of the California general population were 452,63 (62.27%) and 274.31 (31.23%) respectively, $x2$ (1, N=727) = 139.37, $p<.001$.

Since it has already been established that non-Europeans in the world tend to have a lower MS rate than Europeans and European Americans, a second chi-square analysis was performed with the exclusion of the MS patients of non-European ethnicity. By this categorization 607 (89.00%) of the MS patients were in the higher risk group and 75 (11.00%) were in the lower risk group. The numbers expected on the basis of the California general population were 682 (84.74%) and 104 (15.26%) respectively, $x2$ (1, N = 682) = 9.58, $p < .01$. **Table 3** (p. 140) displays the product moment correlation matrix for the variables under consideration-present age, gender, darker eye color, family history of MS severity of the disorder (stage of progression), age at diagnosis, ethnic risk score (latitude of European ancestry), birth latitude, latitude of residence at time of diagnosis, and years since diagnosis. A principle component factor analysis with varimax rotation was carried out with the variables of present age, gender, eye color, family history of multiple sclerosis, disease stage, age at diagnosis, geographical risk score, birth latitude, latitude at time of birth, and year of diagnosis. This original analysis was causing problems with the determinant of the correlation matrix, and therefore the factor analysis used was without years since diagnosis. **Table 4** (p. 140) displays the factor

Table 3. Correlation of gender, eye color, age at diagnosis, severity of the disease, ethnic risk score, birth latitude, residence latitude when diagnosed, years since diagnosis, family history of MS, and present age.

	2	3	4	5	6	7	8	9	10
1. Present age	-.03-	.06*	.08*	.36***	.56***	.18***	.16***	.03	.58***
2. Gender (M = 1, F = 2)		.10**	-.02	-.08*	-.07	.01	.02	-.03	.04
3. Eye Color			.01	.04	-.07	-.33***	-.04	.05	.00
4. Family History of MS				-.01	.07	.03	-.00	-.03	.03
5. Severity of the disorder					.04	.01	.03	.03	.38***
6. Age at diagnosis						.13***	.12**	.15**	.25**
7. Ethnic risk score							.16***	-.05	.08*
8. Birth latitude								.13**	.07
9. Latitude of residence at time of diagnosis									.18***
10.Years since diagnosis									

Note. Gender coded 1 = male and 2 = female; family history of MS coded 1 = yes and 2 = no.
*p < .05, **p < .01, ***p .001

Table 4. Factor analysis summary.

	Factors			
Variable	**1**	**2**	**3**	**4**
Present age	.89	-.08	.03	-.04
Gender	-.04	.13	-.04	.83
Eye color	.06	.80	.04	.22
Family history	.19	.03	-.29	.12
Disease stage	.51	.22	.24	-.10
Age at diagnosis	.74	-.15	-.30	.07
Ethnic risk	.16	-.76	.04	.11
Birth latitude	.29	-.27	.54	.37
Diagnosis latitude	-.03	.10	.80	-.04

analysis summary. There were four factors with an eigenvalue greater than one. Factor 1 had an eigenvalue of 1.87 and accounted for 20.8% of the variance and was labeled "progression of disorder." It's highest factor loadings were with present age, age at diagnosis, and severity of disorder. Factor 2 had an eigenvalue of 1.29, and accounted for 13.2% of the variance, and was labeled "Northern European characteristics." It's highest factor loadings were with eye color and geographical risk score. Fac-

Table 5. Multiple regression summary with dependent variable of disease state (Severity)

Dependent variable	r	R	R2	Beta	F
Present age	.36	.36	.13	.50	107.75**
Age at diagnosis	.25	.42	.17	-.08	75.40**
Gender (M=1, F=2)	-.08	.42	.18	-.26	52.41**

**p <.01

Table 6. Multiple regression summary with dependent variable of age first diagnosed

Dependent variable	r	R	R2	Beta	F
Present age	.56	.56	.32	.63	338.00***
Severity	.04	.59	.35	-.07	196.33***
Latitude of diagnosis	.18	.62	.38	-.20	146.70***
Gender (M = 1, (F = 2)	-.07	.62	.38	-.17	112.41***

***p < .001

tor 3 had an eigenvalue of 1.16, accounted for 12.9% of the variance, and was labeled "latitude." The highest factor loadings were with latitude at diagnosis and latitude at birth. Factor 4 had an eigenvalue of 1.06, accounted for 11.7% of the variance, and was called "gender." The only high factor loading was with gender. Stepwise multiple regression was carried out with the dependent variable of disease stage and the independent variables of present age, gender, eye color, family history of multiple sclerosis, disease at diagnosis, geographical risk score, birth latitude, and latitude at time of diagnosis. **Table 5** (p. 141) contains the multiple regression summary. It is apparent that present age, age at diagnosis, and gender provide a multiple correlation of .42.

Table 6 (p. 141) provides the multiple regression summary regression summary table with the dependent variable of age of onset, a variable that is relevant to the course of some disorders such as schizophrenia and alcoholism. It is apparent that the independent variable of present age, disease stage, latitude lived in at the time of diagnosis, and gender provide a multiple correlation of .62.

Discussion

The fact that the prevalence of multiple sclerosis is apparently greater in Californians of Northern European ethnicity than in those of Southern Europe ethnicity is consistent with the fact that Northern Europeans (in Europe) have a much higher prevalence of MS than Southern Europeans. The present findings suggest that the Northern-Southern European differences are at least in part a function of

genetics. Nevertheless, other explanations such as SES and dietary tradition brought to the United States from Europe cannot be ruled out. The fact that the progression of disorder, years since diagnosis, and present age correlate positively with each other should not be regarded as surprising or extremely important findings. By definition, a progressive disorder is one that gets worse with time.

Gender was a variable that produced noteworthy findings. Male gender was significantly associated with greater severity both in univariate analysis and in the multiple regression. Male gender was associated with older age of onset in the multiple regression. Male gender was associated with lighter eye color. Gender was included as a variable because females have a higher MS prevalence and because the two sexes have symptoms and course differences in some disorders. This variable, however, was regarded as an exploratory one without hypotheses. Nevertheless, gender differences relevant to those of the present study were reported in an English abstract of a Russian language journal. Vein, Voznesenskia and Khromova[18] found that "On the basis of clinical and paraclinical data, including data concerning mental state of patients' disturbances, and intellectual functioning the authors determined that the development of multiple sclerosis in men is atypical as compared with women. In men the disease begins earlier and its course is more malignant without remissions and efficacy of hormone therapy." In both the Russian study and the present one, males had greater severity. The age of onset dependent variable, however, yielded different findings. On the other hand, in a review of the literature by Leibowitz and Alter[19] it was concluded that in females, age of onset tends to be younger and prognosis worse. Some of the correlations suggest that geography may be decreasing in importance as a correlate of MS prevalence.

Age at diagnosis correlated positively and significantly with birth latitude and onset latitude. It is difficult to say whether and how these correlations fit into a larger pattern with the consideration of the positive correlation between ethnic risk and age of diagnosis. There appears to be epidemiological changes in schizophrenia that could somewhat resemble the changes in MS here suggested. Templer, Holcomb, Barthlow, Ayers and Ruff[20] noted the greater seasonality of schizophrenic births in Europe than in the United States over the 20th century and attributed this to the great prosperity and protection from the elements in the United States. On the basis of this technology based explanation Templer and Austin[21] predicted and found a decrease in the seasonality of schizophrenic births from 1900 to 1960 in Missouri. Extrapolation from one disorder to another is usually rather tenuous, but it must be recognized that there is appreciable overlapping geographical prevalence of schizophrenia and multiple sclerosis with both disorders being more common in locations of greater latitude. A correlation of .81 between the prevalence of schizophrenia and multiple sclerosis in the districts of Italy was found.[15] A correlation of .94 was reported between schizophrenia rate and multiple sclerosis rate in the six continents of the world.[14] There are other similarities besides the geographical ones. Templer, Regier and Corgia[13] pointed out that both are chronic familial disorders that begin in early adult life and run an irregular course. With such considerations the present correlation between age and latitude could be understood in terms of older persons having been more vulnerable to the geographical influences of an earlier period of time.

The absence of any seasonality of multiple sclerosis births in contrast to seasonality of MS births in Denmark[16] and Sweden,[17] could also be viewed in terms of a lessened geographical influence as a function of decades of time. In the Denmark

study the patients had 1950-1984 year of onset. In the Swedish study they had year of onset 1900 - 1964. In contrast to these two studies with archival data, the present study used all contemporary MS patients who were, for the most part, born in a later era. It has been extremely well established that MS has a greater prevalence in locations further from the equator. The positive correlation between eye color and ethnic background and the high factor loadings for these two variables on Factor 4 were predicted and predictable. Northern European persons tend to have lighter eye, hair, and skin color than Southern Europeans. his association, however, probably tells us more about the relationship between geography and human physical appearance characteristics than about the etiology of multiple sclerosis. Nevertheless, the fact that Northern Europeans have higher MS rates than Southern Europeans, and the fact that European Americans have higher MS rates than African Americans suggests that searching for morphological correlates of MS and within MS populations would not appear to be an unreasonable endeavor. An interesting and unexpected observation was that in a state with .8% Native American populations, 63 (6.7%) of the MS patients were at least part Native American. Only eight patients (1.1%), however, were one half or more Native American. We do not have adequate basis to infer that the prevalence of MS is high in Native Americans. We can, however, say that having Native American ethnicity certainly does not provide relative immunity from this disorder. The previous literature has stated that the rate is very low. In a review by Acers and Acers-Warn[22] it was said that "Preliminary analysis indicates an incidence rate of five to ten-fold less than that of Caucasian populations in the same geographical areas." (p. 311).

The methodological limitations of this study should be acknowledged so that some of the inferences on the basis of the findings be viewed as tentative rather than conclusive. One limitation is that general population persons in Orange and Fresno counties are probably not identical in ethnic distribution to all Californians. Another limitation is that persons who belong to multiple sclerosis associations may not be representative of all persons with multiple sclerosis. Further, far from 100% of MS patients sent the questionnaires completed and returned them. And the present and the U.S. government determination of ethnicity used for comparative purpose both have imperfections in addition to probably not being identical. These limitations, however, probably apply more to the ethnic distribution findings than to correlation-based analyses and the month of birth analysis. It must be borne in mind that all of the subjects in the present study are multiple sclerosis patients.

It is likely that more findings shedding light on the etiology of MS would be obtained if the same variables, e.g., eye color, used in the present study be employed in comparing multiple sclerosis patients with control non-multiple sclerosis patients. Such research is recommended.

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