Multiple sclerosis frequency in Israel's diverse populations

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Abstract—*Background:* Israel has served for almost half a century as a site for epidemiologic studies of multiple sclerosis (MS). Its small geographic size, well-equipped, accessible, and subsidized health facilities, trained physicians, detailed census data, and a National MS Register, maintained since 1960, offer advantages for accurate determinations of MS frequency in its diverse populations. *Method:* The authors calculated age-specific prevalence of MS in Israeli-born Jewish inhabitants, immigrant Jews from Europe/America and from North Africa/Asia, Israeli-born Christian and Moslem Arabs, Druze, and Bedouins. *Results:* Prevalence rate of MS per 10^5 population on June 30, 2000, for each of these groups in the order listed was 61.6, 53.7, and 27.9 for the Jewish groups and 35.3, 14.7, 10.9, and 17.3 for the non-Jewish groups. Three tiers in MS prevalence were apparent. The highest rates were in Israeli-born Jews and in Jewish immigrants from Europe/America (significantly higher in the former than the latter). Jewish immigrants from African/Asian countries and Christian Arabs had intermediate MS rates (significantly lower than in the first two groups but not significantly different from each other). Moslem Arabs, Druze, and Bedouins had the lowest rates of MS (significantly lower than in the intermediate group but not significantly different from each other). *Conclusion:* Diverse ethnic groups living in the same geographic area may have significantly different frequencies of MS.

NEUROLOGY 2006;66:1061–1066

Geographic differences in the frequency of multiple sclerosis (MS) have been recognized for almost a century.[1-3] Developed regions of the world, in general, show higher rates than developing regions, both in the northern and southern hemisphere.[4] MS frequency may also differ in different ethnic groups living in the same area.[5-14] Such differences in frequency have led to the conclusion that MS has a multifactorial etiology, including both genetic and environmental factors.[15] However, although many hypotheses have been offered,[15-25] the cause of MS has not yet been identified. Determination of MS frequency in different ethnic groups, all living in the same area, helps control for geoclimatic differences and may help identify the environmental risk factors that are most plausible for further study. We describe MS frequency in Israel, a small country with a Mediterranean climate and diverse populations.

Israel's population includes Jewish and non-Jewish groups who have been living for centuries in Palestine. Additional Jews and non-Jewish groups immigrated after the State was established in 1948, increasing the total population 10-fold from about 650,000 at its founding to over 6 million at present.[26] The groups who now live in Israel include the offspring of the indigenous Jewish groups, Moslem and Christian Arabs, Druze and Bedouins, Jewish immigrants from Europe and America, Jewish immigrants from North African, Middle Eastern, and other African/Asian/Pacific countries, among others. According to the national census at the end of 2000,[26] 61.8% of the Jews were native-born, 27.4% were European or American immigrants, and 10.8% were African or Asian immigrants; 81.8% of the Arabs and Druze were Moslem Arabs, 9.4% Christian Arabs, and 8.8% Druze. Non-Jewish immigrants came to Israel mainly from the surrounding Arab countries. All of these diverse groups constitute the Israeli population among whom we estimated MS prevalence. These groups provide opportunities to investigate the effect of environmental factors possibly related to risk of MS.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the April 11 issue to find the title link for this article.

Methods. *Case ascertainment/data collection.* This study was approved by the Helsinki Committee of Israel's Department of Health (akin to an Internal Review Board in the United States). The Israeli National MS Register (INMSR) was established in 1960 by M. Alter with support from the NIH, the National MS Society in the United States, and Israeli Medical Centers. It is maintained by E. Kahana at the Uri Leibowitz Neuroepidemiology Unit, Hadassah Hebrew University Hospital, Jerusalem, Israel, with a duplicate dataset at Barzilai Medical Center, Ashkelon,

*See the Appendix for a listing of members of the Israeli MS Study Group.

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Supported by grant RG3647-A-8, the National Multiple Sclerosis Society of USA.

Disclosure: The authors report no conflicts of interest.

Received August 4, 2005. Accepted in final form December 20, 2005.

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Table 1 *Patients with multiple sclerosis (MS) registered in the Israeli National MS Register and living in Israel on June 30, 2000*

Type of MS diagnosis	Jews born in Israel	Jews born in Europe/America	Jews born in Africa/Asia	Arabs	Total
Definite/clinically definite/probable	1,497	952	248	164	2,861
Possible, n (%)	185 (10.9)	160 (14.3)	83 (25)	8 (4.7)	436 (13.2)
Total	1,682	1,112	331	172	3,297

Israel. Names and identity numbers are accessible only to E. Kahana and her research assistant to maintain privacy and preserve confidentiality. Data on diagnosed patients with MS and those with similar disorders are periodically solicited and received from all general hospitals throughout Israel, 27 MS specialty and neurology referral clinics (see participating centers), the Israeli MS Society, and from the three laboratories in Israel where CSF is assayed for oligoclonal bands. The INMSR regularly inquires about additional cases of MS and other related disorders at each of these sources and, when notified that medical records are ready for review, the records are abstracted using pre-coded forms for computer entry. Duplicates are identified and data on existing MS cases are updated while new cases are added to the INMSR. Death certificates are regularly requested to determine if and when the registered patients with MS died.

Diagnostic criteria for MS. When the INMSR was established in 1960, Allison and Millar's[27] diagnostic criteria for MS were used. Later, the criteria of McDonald and Halliday[28] were introduced and now all patients with MS in the INMSR meet the criteria of Poser et al.,[29] i.e., CNS signs scattered in time and place with or without laboratory support. According to Poser's definition, the following categories of diagnosis are used: definite (histologically verified, although pathology may differ),[30,31] clinically definite (including laboratory supported definite), and probable (including laboratory supported probable). The records of patients with possible MS are retained in the INMSR because, over time, some evolve and meet the diagnostic criteria for probable or even clinically definite MS. When measuring prevalence, only patients with MS who were living on a given date are counted. In the INMSR, the number of definite cases is small because autopsy is religiously discouraged for both Jews and Moslems. However, three patients had a brain or spinal cord biopsy that confirmed MS. Of the 40 autopsy-confirmed definite MS cases in the INMSR, all died before June 30, 2000, the date designated as prevalence day on which the point prevalence of MS per 100,000 population in each ethnic group was calculated.

Analysis. The most recent years of any current survey of MS prevalence underestimate the true prevalence because there is an inevitable delay after onset of symptoms before MS is medically diagnosed. For this reason, ascertainment continued through April 2004 although the prevalence estimate in the present study of MS included only patients diagnosed and living on June 30, 2000: prevalence day. The latter constituted the numerator of our prevalence rates. The denominator of our calculations of prevalence rates included the total population for each of the diverse groups studied, living in Israel on June 30, 2000, based on the official Bureau of Statistics census data.[26]

In the census, Druze are considered a distinct group although they generally regard themselves as Arab. Bedouin, on the other hand, all of whom consider themselves Moslem Arabs, are not counted separately from Arabs in the census so that a national MS prevalence rate for all Bedouin could not be calculated. However, virtually all Arabs living in the Negev region of southern Israel are Bedouin. We had census data for Arabs living in the Negev and MS prevalence that was calculated for the "Arabs" of the Negev was considered the prevalence of MS in Bedouin. Since age distribution differs among the population groups studied and MS prevalence is age-dependent, age-adjusted rates were calculated, using the direct adjustment method. In order to allow comparisons with our previous Israeli studies, the same standard population as in our earlier studies was used for the age adjustment, vs the Israeli Jewish population on December 31, 1960.

Results. The INMSR had registered 5,294 patients with MS by April 2004, when ascertainment was completed. After excluding those who died before prevalence day, those with onset after prevalence day and those who immigrated to Israel after prevalence day, the total number of patients with MS alive in Israel on prevalence day was 3,297. Table 1 shows the distribution of these definite, clinically definite, and probable patients with MS by ethnic group and classification category. Also, the number and proportion of patients with possible MS is shown.

Age distribution of the patients with MS by decades and the population at risk in each decade is shown for the Jewish population in table 2 and for the Christian and Moslem Arabs, Druze, and Bedouin Arabs in table 3. Age-adjusted prevalence rates of MS per 100,000 population

Table 2 *Age distribution of multiple sclerosis (MS) by decades in the Jewish populations of Israel on June 30, 2000*

	Place of birth						
	Israel		Europe or America		Africa or Asia		Total
Age, y	N	Population	N	Population	N	Population	N
0–9	1 (1)	827,200	0	54,100	0	6,600	1 (1)
10–19	17 (1)	697,300	6	147,400	1	19,900	24 (1)
20–29	250 (27)	626,000	91 (7)	176,400	3	21,900	344 (34)
30–39	409 (39)	429,900	173 (12)	173,500	25	38,800	607 (51)
40–49	487 (53)	356,200	264 (30)	196,200	63 (16)	97,800	814 (99)
50–59	244 (38)	135,500	255 (52)	195,200	96 (27)	152,200	595 (117)
60+	89 (26)	93,100	163 (59)	459,200	60 (40)	218,400	312 (125)
Total	1,497 (185)	3,165,200	952 (160)	1,402,000	248 (83)	555,600	2,697 (428)

Numbers shown include histologically proven, clinically definite, and probable MS cases, with possible MS cases in parentheses.

Table 3 *Age distribution of multiple sclerosis (MS) by decades in the Arab populations of Israel on June 30, 2000*

	Christian Arabs		Moslem Arabs		Druze		Bedouins		Total
Age, y	N	Population	N	Population	N	Population	N	Population	N
0–9	0	22,300	0	300,000	0	25,600	0	74,200	0
10–19	1	19,500	1	202,100	1	21,900	0	17,600	3
20–29	6	18,900	23	171,200	2	20,200	1	5,300	32
30–39	11	16,600	36 (2)	125,000	2	14,400	3	6,600	52 (2)
40–49	11	12,800	27 (2)	73,600	1	9,400	0	3,600	39 (2)
50–59	9	8,900	15	41,900	2	5,000	2	2,400	28
60+	5 (2)	111,000	4 (1)	38,400	1 (1)	5,800	0	1,400	10 (4)
Total	43 (2)	210,000	106 (5)	952,200	9 (1)	102,300	6	111,100	164 (8)

Numbers shown include histologically proven, clinically definite, and probable MS cases, with possible MS cases in parentheses. Place of birth of all Arabs included was reported to be Israel.

are shown in table E-1 (on the *Neurology* Web site at www.neurology.org). Based on the definite, clinically definite, and probable MS cases, the age-adjusted prevalence rate was 61.6 among Israeli-born Jews and 53.7 among Jews born in Europe/America who immigrated to Israel. These rates are each higher than the rates in all the other population groups ($p = 0.000$), with the rate in Israeli-born higher than among Europe-America immigrants ($p = 0.002$). The prevalence rate for Jewish immigrants from Arab countries of Africa/Asia was 27.9, i.e., about half the prevalence rate of MS among Israeli-born Jews and among Jews born in Europe/America ($p = 0.000$). Among Christian Arabs, the rate of MS was 35.3, not significantly different from the rate among Jewish immigrants from African/Asian countries, but higher than among Moslem Arabs ($p = 0.001$), Druze (0.000), and Bedouin ($p = 0.056$). Among Moslem Arabs, all of whom were born in the Middle East, the rate was 14.7, about half the rate among Jews born in the Arab countries of North Africa and Asia Minor and about 42% of the rate among Christian Arabs. Among Druze, who live mainly in the Galilee in northern Israel, the prevalence rate was 10.9 and in Bedouin from the Negev in southern Israel, it was17.3. However, the small number of patients with MS in the Bedouin group renders the CI of their rate fairly large. The rates of MS among Moslem Arabs, Druze, and Bedouins were not significantly different.

In the figure, three groups may be discerned when ranking MS prevalence rates: 1. Israeli-born Jews and Jewish immigrants from Europe/America had the highest rates. 2. Jewish immigrants from Africa/Asia and Christian Moslems had intermediate rates (while not different from each other, the rates were significantly lower than in Group 1 and significantly higher than in the subsequent group). 3. Moslem Arabs, Druze, and Bedouin had the lowest prevalence rate of MS, not different from each other but significantly lower than in Groups 1 and 2.

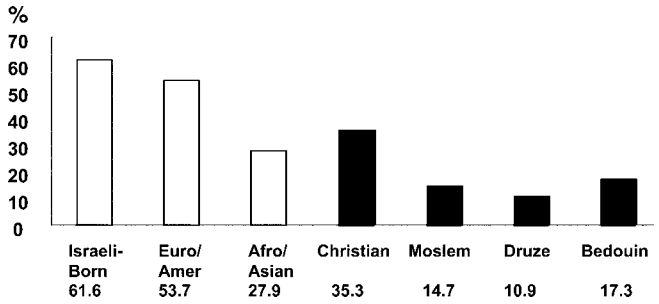

Figure. Multiple sclerosis prevalence in Israel's diverse populations: rate/100,000 population.

Systematic deferral of follow-up or delayed performance of all the testing needed to confirm the diagnosis of clinically definite and probable MS might lead to a longer time that a diagnosis of possible MS is retained and thus a lower rate of definite or probable MS for a particular group. Since there were differences in the percentage of possible MS among the ethnic groups (table 1), we checked whether it could explain differences in rates between population groups. We found that, even with possible cases added (table E-1), the difference in the prevalence rates among groups remained similar and the significance of the differences in prevalence rate between the groups was virtually the same.

Discussion. When frequency of MS among ethnic groups is reported, it is important to show that differences are not simply a reflection of accessibility to medical facilities. For many reasons, it is unlikely that the ethnic differences in MS prevalence in Israel are attributable to such a bias. A liberal immigrant acceptance policy for Jewish immigrants allowed entry into Israel of even the infirm and aged. Several of the same investigators have studied MS epidemiology in Israel since the early 1960s[32] and differences among the Jewish ethnic groups have been consistent over time.[33] The INMSR now includes virtually all MS cases diagnosed in Israel from 1950 through April 2004. Jewish and Arab neurologists and general practitioners participated in recruitment of patients with MS. All citizens of Israel have ready access to medical facilities at minimal cost or as an employee benefit because health care is substantially subsidized by the Israeli government. The medical facilities are considered excellent on an international standard and are well distributed geographically with easy referral to secondary and tertiary care centers. Each medical center has well-

trained and experienced neurologists who use modern imaging techniques to aid in diagnosing MS. Thus, case ascertainment is likely to be complete and the diagnoses accurate. Moreover, a network of MS experts in Israel has formed the Israeli MS Study Group (see participating centers at the end of this article) that meets regularly for seminars and case presentations. This helps assure a high, reasonably uniform quality of diagnosis of MS throughout the country.

MS prevalence rates in Israel's diverse population groups differed considerably, particularly when comparing Jewish immigrants from Europe/America and Israeli-born Jewish groups, on the one hand, and Jewish immigrants from Africa/Asia, Christian Arabs, Moslem Arabs, Druze, and Bedouins inhabitants of Israel, on the other hand. Such differences might be due to genetic or environmental factors or both. The differences in prevalence of MS are very unlikely to be attributable to bias in case ascertainment as discussed. Also, Israel's small size facilitates obtaining multiple medical opinions in different medical centers. This is true for all ethnic groups, including the non-Jewish groups and Jewish immigrants from Africa/Asia among whom MS was less frequent.

MS frequency also appears to be low in Arab countries of the Middle East. In Jordan, MS prevalence was $20/10^5$ population.[34] This rate was based on only a small number of native-born Jordanian patients with MS and the 95% CI of the estimate was wide (9.5 to 47.2), but, even at the high end of this CI, prevalence was still lower than the rate among Jews born in Israel and among European and American Jewish immigrants to Israel. In Kuwait, MS prevalence was $4.4/10^5$ if limited to native-born Kuwaitis.[35] A later study based only on Kuwaitis[36] reported a rate of $9.5/10^5$, close to what we observed in Moslem Arabs, Druze, and Bedouin. Among Palestinians living in Kuwait, the rate reported was $23.8/10^5$, similar to the MS rate among Jewish immigrants to Israel from African/Asian countries. In Saudi Arabia,[37] the MS frequency was $8/10^5$ based on 16 patients ascertained between 1983 and 1986. In Iraq,[38] it was $3.4/10^5$ and in Tunisia, it was between 3.3 and $10/10^5$.[39] This series of studies, all of which showed low rates in Arabs, strengthens the likelihood that the low MS rates that we observed in Israel in Moslem Arabs, Druze, and Bedouin are accurate and truly lower than the rates observed in Israeli-born Jews and Jewish immigrants to Israel from Europe/America.

MS prevalence in Jewish immigrants to Israel from Arab countries appears to be close to the rates of MS in the Arab countries, as cited above, but, as previously determined,[33] the offspring of African/Asian immigrant Jews, who were born and reared in Israel, had a higher age-adjusted MS rate of $51.3/10^5$, similar to the prevalence rate of $68.5/10^5$ in Israeli-born offspring of European/American Jewish immigrants. The rate of MS in the offspring of Jewish African/Asian immigrants born and reared in the Israeli environment was almost twofold higher than in Jewish African/Asian immigrants found in the present study (i.e., $27.9/10^5$). This increase in virtually one generation would appear to implicate an environmental factor rather than a genetic cause. Nonetheless, genetic factors related to MS need to be studied[40-42] in order to define more thoroughly both the genetic and environmental differences among Israel's Jewish and non-Jewish patients with MS. Also, clinical characteristics of MS among the different ethnic groups in Israel that we are currently evaluating, need to be compared among the different ethnic groups.

Recent reports of possible environmental risk factors of MS may be examined in light of our observations regarding MS frequency in different ethnic groups to see whether postulated etiologic factors can explain the observed frequency differences. One recent report[21] implicated a protective role for actinic exposure by noting that skin cancers (but not other cancers) were significantly less common in patients with MS than in matched controls, implying that patients with MS had had less exposure to sunlight. The increasing gradient of MS frequency with latitude has also been attributed to the decreasing gradient of actinic radiation exposure with increasing latitude north and south of the equator.[10] In other recent studies, vitamin D, a potent regulator of immune responses, is formed in the skin by exposure to sunlight and has been reported to be deficient in some patients with MS.[22,43-45] When added as a food supplement, vitamin D has been reported to improve symptoms of MS,[46] decrease the exacerbation rate,[46] and enhance immunologic self-tolerance.[47]

However, the actinic exposure hypothesis (and, by inference, vitamin D) would not explain why Jews of African/Asian ancestry who were born and reared in Israel have a higher MS rate than their immigrant forebears because both Africa and Asia (whence Jews migrated) and Israel have abundant sunshine almost all year. Moreover, why would Jews born in Israel's sunny clime have higher rates of MS than Arabs born and reared in the same area? Are Arabs exposed to more sunlight than Jewish inhabitants? Are Moslem Arabs exposed to more sunlight than Christian Arabs? Thus, our observation on differences in MS frequency in different ethnic groups in Israel pose difficulties for accepting that actinic exposure and vitamin D alone play a determining role in preventing MS. The hypotheses that exposure to sunlight and intake of vitamin D prevent MS need to be refined.

Similarly, infections, especially those that occur in childhood, have been postulated to be factors in determining risk of MS.[48,49] Age at which childhood infections are acquired is, on average, older in regions with higher rates of MS,[49-51] but other diseases may be exceptions.[52] For MS, it is postulated that early infection may lead to increased immune self-tolerance and decreased risk.[53,54] In large families,

childhood infections tend, on average, to occur earlier as older children may bring home illnesses that infect younger children. African/Asian Jewish immigrants, Moslem Arabs, Druze, and Bedouins in Israel tend to have larger families (and a lower rate of MS) than Israeli-born Jewish offspring of the African/Asian immigrants and European/American immigrants. Total fertility per woman measured recently[41] was 5.37 children per woman in Arab countries (where MS has a low frequency) compared to 3.71 children per woman in more developed countries. Census data from Israel for 2000[55] also tend to support an inverse association between family size and MS frequency. Total fertility (i.e., the average expected number of children/woman in her lifetime) in Israel was 2.66 for all Jews, 2.55 for Christian Arabs, 3.07 for Druze, and 4.74 for Moslem Arabs. The total fertility of all Jews includes the ultra-orthodox who tend to have large families but MS frequency in that group has not yet been independently determined. Such a study might provide a test for the hypothesis that large families (and early infections in childhood) influence risk of MS. These examples, while speculative, illustrate how data on MS frequency in Israel's diverse populations might help unravel the genetic and environmental factors contributing to the cause of MS.

Appendix

By contributing the patients with MS at their center, the Israeli Multiple Sclerosis Study Group made this study possible. Participating multiple sclerosis centers by key person at each center. Key person in alphabetical order is as follows: Oded Abramsky, MD, PhD—Hadassah Medical Center; Anat Achiron, MD, PhD—Sheba Medical Center-Tel Hashomer; Irina Bloch, MD—Emek Central Hospital; Joab Chapman, MD, PhD—Sheba Medical Center-Tel Hashomer; Olga Chilkevitzh, MD—Ichilov Hospital; Ibrahim El Said, MD—Soroka Hospital; Yoram Finkelstein—Shaarei Tsedeq Hospital; Slomo Flechter, MD—Assaf Harofe; Ronit Gilad, MD—Wolfson Hospital; Manfred Green, MD—Israeli Center for Disease Control (ICDC); Bella Gross, MD—Western Galilee Hospital, Nahariya; Arnon Karni, MD—Ichilov Hospital; Dimitry Karussis, MD, PhD—Hadassah Medical Center; Isabelle Korn-Lubetzki, MD—Formerly at Bikur Cholim Hospital; Edna Kott, MD—Formerly at Meir Hospital; Larissa Lessin, MD—Meir Hospital; Rafik Massalha—Soroka Hospital; Ron Milo, MD—Barzilai Medical Center; Ronit Mosberg-Galili, MD—Beilinson Medical Center; Puyo Nisipeanu, MD—Hillel Yaffe Hospital; Hana Rawashdeh, MD—Carmel Hospital; Radi Shahien, MD—Rivka Ziv Hospital, Zefat; Waleed Simri, MD—Western Galilee Hospital, Nahariya; Ludmila Toriansky, MD—Barzilai Medical Center; Svetlana Veldman, MD—Soroka Hospital; Boaz Weller, MD—Bnai Zion Hospital; David Yarnitsky, MD—Rambam Hospital.

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