PAPERS AND ORIGINALS

Multiple sclerosis among immigrants in Greater London

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British Medical Journal, 1976, 1, 861-864

Summary

Among immigrants resident in greater London from Europe, Ireland, the USSR, the old Commonwealth countries of Australia, Canada, and New Zealand, North and South America, Egypt, Turkey, and Iran the incidence of admission to hospital for probable multiple sclerosis (MS) between 1960 and 1972 was high or moderately high. The incidence was of the same order as that found in those born in the United Kingdom. Immigrants from India, Pakistan, and other Asian countries and from new Commonwealth Africa and America, which includes the West Indies, had a low incidence of hospital admission for MS. Immigrants from countries where the risk of MS is low whose parents were born in Europe had a reduced incidence of admission to hospital but not the very low incidence found in those whose parents were also born in these countries. Emigrating to England from low risk parts of the world did not seem to increase the risk of developing MS.

Introduction

The incidence of multiple sclerosis (MS) varies throughout the world.[1] For instance, Europe, Canada, and the northern parts of the United States are areas of high risk, whereas the new Commonwealth countries of Asia, Africa, and America (the West Indies) are low-risk areas.[2] Those who migrate from a high-risk area to a low-risk area keep their high risk unless they migrate below the age of 16.[3-5] The area of residence during childhood therefore seems to be of great importance in deciding the risk of developing MS, which is strong evidence that the disease is related to the childhood environment. We have therefore undertaken a study to find out what happens to those who migrate from areas where the incidence of MS is low to an area where the incidence is high.

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Method

More than half of the new Commonwealth immigrants to England have settled in greater London and in the west Midland conurbation (54·5%). These are nearly all immigrants from areas where the risk of MS is low (table I). There are considerable differences in the age distribution of different groups of immigrants. For instance, immigrants from the new Commonwealth countries are on the whole younger than those from Europe. The United Kingdom-born population of greater London was, therefore, used as the standard and the age specific expected numbers of patients with MS for the different immigrant groups were calculated using the age distribution of those born in the United Kingdom and of the immigrant populations at risk.

The 1966 10% census of population, a mid-point between 1960 and 1972, was used for the populations at risk. The age distributions of the immigrant populations in 1966 were not available and were estimated by using the age distribution for the different immigrant groups at the 1971 census. Similar calculations for the immigrant groups by the birthplace of parents at the 1966 census were prepared by the Office of Population Censuses and Surveys.

Since April 1969 birthplace has been included on death certificates in the United Kingdom and the Registrar General's department has provided copies of the death certificates of immigrants who died with a diagnosis of MS on part 1 of the certificate.

The medical research committees of all the London teaching hospitals and the hospitals in the West Midlands, Bradford, and Leicester were asked for permission to study the case records of all inpatients from 1960 to 1972 diagnosed as having MS. All the hospitals and neurologists agreed to take part. For the non-teaching hospitals who did not have a diagnostic index computer listings of cases of MS were obtained from the Hospital Activity Analysis Scheme. The case folders of the patients were studied and we accepted the diagnosis of the neurologists on whether the patient had MS or probable MS or whether the diagnosis was in doubt. First admission to hospital usually occurred when MS was suspected so that further investigation could be undertaken.

The histories of the patients were studied to find their birthplace. When the patient's birthplace was in doubt we sought the help of the patient's family doctor. Often the patient had moved and the new

TABLE I—*Numbers of new Commonwealth immigrants to England and Wales*

	Asia	America	Africa	Europe	All new Commonwealth	% of England and Wales 1966
England and Wales						
1961 census	270 495	172 379	42 799	33 331	519 004	
1971 census	617 880	302 485	158 255	42 820	1 121 440	
1966 10% sample	42 987	26 862	8 851	4 265	82 965	44·3
Greater London	16 201	15 189	4 199	1 181	36 770	
West Midland conurbation	4 451	3 580	323	86	8 440	10·2
Remainder of west Midlands	1 816	610	263	95	2 784	3·4
Bradford	1 101	91	37	9	1 238	1·5
Leicester	698	285	99	16	1 098	1·3
Total	24 267	19 755	4 921	1 387	50 330	60·7

TABLE II—*Patients admitted to hospital with probable MS 1960-72—Greater London residents*

Place of birth	Population 1966 census 10% sample		Patients first admitted 1960-72 (and age-specific expected number at UK-born rates)			All patients admitted 1960-72
	Male	Female	Male	Female	Total	
UK (including Northern Ireland)	318 626	348 688	1 316	2 228	3 544	3 895
Europe	7 802	11 318	50 (48·1)	102 (110·0)	152 (158·1)	173
Irish Republic	11 715	13 409	54 (82·5)	114 (142·8)	168 (225·3)	179
Old Commonwealth	1 581	1 994	6 (8·5)	11 (16·3)	17 (24·8)	18
New Commonwealth America	7 647	7 542	5 (54·0)	11 (76·0)	16 (130·0)	17
New Commonwealth Africa	2 479	1 720	2 (13·6)	2 (12·2)	4 (25·8)	4
New Commonwealth Asia and Oceania:						
Sri Lanka	371	256	0 (2·4)	0 (2·4)	0 (4·8)	0
Cyprus	2 438	2 062	11 (15·4)	12 (19·6)	23 (35·0)	23
India	4 488	3 535	3 (29·2)	9 (32·8)	12 (62·0)	13
Pakistan	1 188	411	0 (7·5)	1 (3·2)	1 (10·7)	1
Other	794	658	0 (4·1)	0 (3·9)	0 (8·0)	0
New Commonwealth Asia and Oceania excluding Cyprus	6 841	4 860	3 (43·4)	10 (42·3)	13 (85·7)	14
New Commonwealth Europe (Gibraltar, Malta, and Gozo)	657	524	0 (3·9)	0 (4·5)	0 (8·4)	0
America (USA and South America)	1 190	1 300	5 (6·3)	7 (10·2)	12 (16·5)	14
Burma	224	276	1 (1·4)	0 (2·5)	1 (3·9)	1
China	163	159	0 (1·2)	0 (1·6)	0 (2·8)	0
South Africa	697	826	1 (4·1)	2 (7·4)	3 (11·5)	3
USSR	643	730	2 (3·0)	2 (4·1)	4 (7·1)	6
Elsewhere (Iran, Egypt, Turkey, Other)	1 431	1 348	3 (8·1)	10 (11·5)	13 (19·6)	15
Total residents born outside UK	45 508	48 068	143 (293·3)	283 (461.0)	426 (754·3)	467
Birthplace not stated	1 511	2 076				
All countries of birth (except visitors)	365 654*	398 846*	1 459	2 511	3 970	4 362
Visitors to UK	1 408	1 214				
Total	367 062	400 060				

*Remainders where numbers are very small have been omitted.

doctor was traced through the family practitioner committees or through the National Health Service Central Register.

In spite of every effort a few patients remained untraced and no doubt a few patients have been wrongly classified as having been born in the United Kingdom.

Results and comment

Seven thousand records of patients who had been admitted to hospital in greater London and the surrounding areas and had been discharged with a diagnosis of MS or probable MS during the 13 years 1960-72 were studied. Few patients had been admitted to more than one hospital and the 7000 records represented 6631 patients; of these 2889 (1133 male and 1756 female) patients had been investigated at the National Hospitals for Nervous Diseases, Queen Square and Maida Vale (44%). Of the 6631 patients 4362 lived at the time in greater London, and they included 467 (10·7%) immigrants. Because MS may cause prolonged disablement and because the number of immigrants from the new Commonwealth has increased greatly, and severely disabled persons might not migrate, we aimed to study the incidence of first admissions of newly diagnosed cases based on hospital folder numbers starting in January 1960. Altogether 392 of the patients admitted had folder numbers preceding 1960 (9%) because they had been previously admitted for symptoms of MS or for some other reason. If these are excluded there were 3970 first admissions among people living in greater London. Of these 3970 patients 426 (10·7%) were immigrants.

The average annual incidence of newly diagnosed MS among hospital patients resident in greater London during the 13 years was four per 100 000. Copies of the case summaries for the immigrant patients with MS were obtained from the hospitals for future reference. Visitors to the United Kingdom diagnosed as having MS were not included and will be reported separately.

The results, as observed and expected numbers of cases, are shown in table II in broad groupings by countries of birth. There was a very low ratio of observed to expected cases in immigrants from the new Commonwealth countries of Africa, Asia except Cyprus, America, and Europe, the ratios of observed to expected numbers being, respectively, 4:25·8, 13:85·7, 16:130·0, and 0:8·4.

Of the four patients with MS from new Commonwealth Africa, two were Asians, one an African, and one of European parents. In new Commonwealth Asia, excluding Cyprus, 12 were born in India and one was born in Pakistan. No patients were born in Sri Lanka or the other new Commonwealth Asian countries (expected 4·8 and 8·0 respectively). One patient was born in Burma, of Spanish forebears (expected 3·9), and none were born in China (expected 2·8). All three patients born in South Africa were English-speaking Whites (expected 11·5). The places of birth of the patients born in new Commonwealth America are shown in table III. Five further patients from the new Commonwealth American countries who were first diagnosed as having MS were later diagnosed as having West Indian neuropathy.

No patients with MS were born in Gibraltar or Malta and Gozo (expected 8·4). This was surprising because immigrants from other Mediterranean countries have a medium risk of MS. According to Dench some Maltese in London pass as Italians.[6]

One hundred and fifty-two patients had been born in Europe (expected 158·1). Immigrants from Spain had significantly fewer admissions for MS than expected ($P > 0.05$), but in the other countries of Europe the differences were not significant (table IV).

There were 168 patients born in the Republic of Ireland (or in a part of Ireland not stated) (expected 225·3). A few patients born in Ireland may have been included among those born in the United Kingdom, but there is no reason for believing that the prevalence of MS in the Republic of Ireland differs greatly from that in England and Wales.[7]

Of the 17 patients admitted from the old Commonwealth countries nine were born in Australia, four in New Zealand, and four in Canada and the numbers of London residents from these countries in 1966 were about 16 880, 6420, and 12 450 respectively. Seven patients were born in the United States and five in Central or South America and the numbers of London residents from these areas, ages unknown,

TABLE III—*Numbers of patients with MS from new Commonwealth America resident in Greater London*

	10% sample from census population 1966			Patients with MS 1960-72 (age-specific expected number in brackets)		
	Male	Female	Total	Male	Female	Total
West Indies:	5 889	5 920	11 809	4 (41·6)	7 (59·6)	11 (101·2)
Guyana	835	839	1 674	1	3	4
Jamaica	3 934	3 998	7 932	2	3	5
Barbados	662	605	1 267	1	1	2
Trinidad and Tobago	458	478	936	0	0	0
Other countries in new Commonwealth America	1 758	1 622	3 380	1 (12·5)	4 (16·3)	5 (28·8)
All new Commonwealth America	7 647	7 542	15 189	5 (54·1)	11 (75·9)	16 (130·0)

TABLE IV—*Actual and age-specific expected MS among immigrants from Europe resident in greater London*

Birthplace	Actual No (and expected number at UK-born rates)		
	Male	Female	Total
	50 (48·1)	102 (110·0)	152 (158·1)
Germany	3 (5·8)	31 (23·4)	34 (29·2)
Italy	12 (9·6)	12 (17·6)	24 (27·2)
Poland	18 (12·5)	7 (12·9)	25 (25·4)
Austria	1 (2·2)	8 (8·8)	9 (11·0)
France	4 (1·9)	7 (7·9)	11 (9·8)
Belgium and Luxembourg	0 (0·7)	2 (3·2)	2 (3·9)
Netherlands	1 (1·3)	2 (3·0)	3 (4·3)
Hungary	3 (2·6)	4 (3·5)	7 (6·1)
Spain	0 (4·3)	8 (12·1)	8 (16·4)
Other Europe	8 (7·2)	21 (17·6)	29 (24·8)

in 1966 were about 19 000 and 5900 respectively. Of the 23 patients born in Cyprus (35 expected; $P>0.05$) 17 were Greek Cypriots and six were Turkish Cypriots.

Thirteen patients with MS were born in the remaining countries (expected 19·6): four were born in Egypt of European parents out of 8500 immigrants from the United Arab Republic; two were born in Turkey out of 3690 immigrants; and three were born in Iran out of 4000 immigrants (1966 census). Of the remaining four patients one was born in the Sudan (of Armenian parents), one in Iraq (of British parents), one in Tunis, and one in Morocco.

Birthplace of parents—The actual number of patients diagnosed as having MS was compared with the age-specific expected number for immigrants from India, Pakistan, and the new Commonwealth countries of Africa and America according to the birthplace of the parents. The results are shown in table V. There were no patients born in Pakistan with both parents born there. Apart from the five Anglo-Indians there was one Indian and one Parsee with both parents born in the new Commonwealth. There was one patient born in Pakistan whose parents were born in the British Isles. Of the 16 patients from new Commonwealth America one had both parents born in the British Isles and one had one parent born in England and one born in the West Indies. For all those patients with both parents born in the new Commonwealth countries the expected number with MS was eight times the actual number of patients with MS.

Relation between onset of MS and immigration—Thirty-seven patients resident in greater London had migrated to England from India, Pakistan, Burma, South Africa, new Commonwealth Africa, and new Commonwealth America and the expected number from these countries was 243·9 (table II). In 11 of the 37 the onset of MS had occurred before they immigrated; their mean age at the onset of symptoms was 30·7 years and the mean age at immigration was 38·1 years. The remaining 26 patients had a mean age of onset at 30·4 years and a mean age at immigration of 22·7 years. In south-east England 65% of all immigrants from the new Commonwealth countries immigrated before the age of 25 in 1970 and 1971 (1971 census). As the mean age of onset of MS among these immigrants from low-risk zones was 30 years most of the 37 patients would be expected to develop their first symptoms after immigrating to England, which was the case in 26 of the 37 patients.

Deaths among immigrants—Multiple sclerosis is coded as the cause of death in only some patients known to have had MS. For instance, in a random sample of 168 patients with MS in this study who have since died multiple or disseminated sclerosis was mentioned in part I of the death certificate in 74 patients (44%), in part II of the certificate, as a contributory cause of death, in 45 patients (27%), and not mentioned at all in 49 patients (29%). According to part I of their death certificates 174 immigrants resident in England and Wales died from MS between April 1969 and the end of 1973. In greater London 59 of the 174 immigrant deaths occurred during this period and 48 of them had been in hospital between 1960 and 1972 at the hospitals whose records we had studied. There were no deaths from MS among people of African, Pakistani, or entirely Indian origin. We had no direct way of estimating the expected number by ethnic background based on population, but the Office of Population Censuses and Surveys divided the records of deaths of people born in the Indian subcontinent into those of Indian and those of British background by examining their names. There is no population at risk for these records so an age/sex standardised proportional mortality was calculated on the deaths in England and Wales. This calculation yielded 17 expected deaths from MS in immigrants with Indian or Pakistani names out of the expected 29·9 for all immigrants from the Indian subcontinent for the five-year period, and, in fact, there were no deaths among immigrants from India with Indian or Pakistani names, an obviously highly significant difference. There were three deaths due to MS among immigrants born in the West Indies (expected 18·1).

TABLE V—*Birthplace of parents. Results are actual and age-specific expected number (in parentheses) of hospitalised patients with MS resident in greater London 1960-72*

Parent's birthplace	Patient's birthplace			
	India and Pakistan	New Commonwealth		Total
		Africa	America	
Both in British Isles	2 (6·0)	0 (1·7)	1 (0·5)	3 (8·2)
One in British Isles	2 (5·4)	0 (0·9)	1 (0·9)	3 (7·2)
Both in new Commonwealth	7*(57·2)	3 (20·1)	14 (112·2)	24 (189·5)
Both elsewhere	1 (1·7)	1 (0·8)	0 (1·7)	2 (4·2)
Birthplace not stated	1 (2·7)	0 (1·1)	0 (14·6)	1 (18·4)
Total	13 (73·0)	4 (24·6)	16 (129·9)	33 (227·5)

*Including five who were descendants of mixed British and Indian forbears.

Discussion

Our findings have shown that, just as those who migrate from areas where the risk of MS is high to lower-risk zones keep their high risk of MS unless they migrate before the age of 16,[3-5] so those who migrate from low-risk countries to London, a high-risk area, keep their low risk of developing the disease; immigrating to England does not seem to increase their risk of MS. Immigrants from low-risk zones whose parents were also born there have a lower risk of being admitted to hospital with MS than those whose parents were born in high-risk zones. Most immigrants with MS born in Asia and Africa had European forebears. Among those with MS there was only one Indian, one Parsee, no Pakistanis, one African, and two Africans of Asian forebears with both parents born in the new Commonwealth. The low hospital morbidity for MS among those born in low-risk countries was confirmed by a study of the deaths among immigrants due to MS from 1969 (April) to 1973. During this time there were no deaths from MS reported among the Indians, Pakistanis, or Africans. Thus MS contrasts, as regards both admissions to hospital and deaths, with another neurological condition, motor neurone disease, which will be the subject of a future report.

It will soon be possible to study the incidence of MS among the United Kingdom-born children of immigrants from low-risk parts of the world to see if their risk of MS is that of their parents or if it increases towards the higher risk that occurs in

England. Such a study would distinguish further between racial and environmental factors. We now have a panel of patients with MS resident in greater London and elsewhere in England who were born in low-risk areas of the world and who, in spite of their group's low risk, have nevertheless developed the disease. Perhaps these patients have some special genetic or environmental characteristics which have predisposed them to develop MS. It would be valuable to study them fully and to search for possible genetic predisposing factors such as the HLA-3-7 and other antigens and obtain a full history of their environmental background.

Multiple sclerosis is highly prevalent where the standard of hygiene is high and in this respect it resembles adult paralytic poliomyelitis before the introduction of the Salk and Sabin vaccines.[8 9] Our findings provide evidence that immunity to MS normally develops in childhood in the low-risk zone and persists when the person moves to an area where MS is highly prevalent. It is suggested that this is because of an early childhood infection by the agent responsible for MS in low-risk zones, probably a virus, which is followed by immunity to the adult form of the disease. The key to the mystery of multiple sclerosis appears to be within our grasp.

This study has been possible only because of the wholehearted co-operation of the staffs of the medical records departments of many hospitals over five years. We would like to thank the neurologists who have allowed us access, with the approval of the medical research committees, to the patients' records. Two neurologists helped with this study: Dr Robert Currier, on sabbatical leave from the University of Mississippi Medical Centre, and Dr Marta Elian of the Midland Centre for Neurosurgery and Neurology. We would also like to thank all the general practitioners who co-operated with the study, the staff of the Office of Population Censuses and Surveys, the family practitioner committees, the National Health Service Register, Southport, and the metropolitan regional hospital boards. Several senior medical students, in particular, Mr Derick Wade and Mr Simon Rideout, helped us with the study. Dr F Anderson of the computer department, University College, Dublin, undertook the computer analysis. Mr Richard Peto, reader in cancer studies, University of Oxford, helped us with statistical advice. The Medico-Social Research Board of Ireland provided facilities for the study.

This study was supported by a research grant from the Multiple Sclerosis Society of Great Britain and Northern Ireland.

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Treatment of overt meningeal leukaemia in children: results of second MRC meningeal leukaemia trial

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British Medical Journal, 1976, 1, 864-867

Summary

After induction of meningeal remission by a course of intrathecal methotrexate patients were randomly allocated to receive either cranial irradiation or craniospinal irradiation. Patients being treated for their first meningeal relapse were randomised separately from those in their second or subsequent relapse. All eight patients in their first relapse who were given cranial irradiation alone developed further meningeal recurrence (median length of remission 15 weeks) compared with only two out of nine given craniospinal irradiation (median length of remission at least 99 weeks). Four of the nine patients given craniospinal irradiation were alive and without further meningeal relapse two and a half to four years after treatment. Craniospinal irradiation produced no such advantage for patients entering the trial in their second or subsequent meningeal relapse. Toxicity was acceptable, and no patients developed encephalopathy. Craniospinal irradiation after meningeal remission induced by intrathecal methotrexate therefore provides a practical means of treating children in their first episode of meningeal leukaemia. None of the patients had received previous CNS irradiation and it remains uncertain whether similar results will be obtained in patients developing meningeal leukaemia in spite of cranial irradiation given as CNS prophylaxis early in the disease.

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Introduction

Conventional intrathecal methotrexate treatment alleviates the symptoms of meningeal leukaemia and clears blast cells from the cerebrospinal fluid (CSF) in a high proportion of patients, but the subsequent meningeal remission is short-lived. Without further treatment of the central nervous system (CNS) blast cells reappear in the CSF after a median interval of 16 weeks (range 11-26 weeks).[1] The value of CNS irradiation given shortly after induction of meningeal remission by intrathecal methotrexate has been investigated in a co-operative randomised trial conducted by the MRC Working Party on Childhood Leukaemia. The trial was designed to determine whether the spinal component of craniospinal radiotherapy contributes to the length of subsequent meningeal remission (fig 1).

Trial

Criteria for admission—To be admitted into the trial patients had to have acute lymphoblastic leukaemia with a newly-diagnosed meningeal relapse and more than $0{\cdot}01 \times 10^9$ mononuclear cells/litre ($10/mm^3$) in the CSF in the absence of an infecting organism, some of the cells