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Migration and multiple sclerosis: The French West Indies experience

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Abstract

The French West Indies (FWI), i.e., the islands of Martinique and Guadeloupe, have recently experienced the emergence of multiple sclerosis (MS). This epidemiological upheaval followed a return migration of the FWI population that had previously migrated to continental France. The prevalence MS was $14.8/10^5$ (95% CI: 11.9–17.7) on Dec. 31, 1999 and its mean annual incidence was $1.4/10^5$ (95% CI: 1.0–1.8) for the period July 1997 to June 2002. The prevalence of MS in Martinique, that received more return migration, is higher than that of Guadeloupe ($21.0/10^5$ *vs.* $8.5/10^5$). This emergence of MS has been accompanied also by an inversion of its clinical spectrum, with recurrent neuromyelitis optica accounting for only 17.8% of cases. The standardized ratio of the incidence of MS among migrants is 1.71 (95% CI: 1.19–2.38; $P<0.01$) and if migration to continental France occurred before the age of 15 it is 4.05 (95% CI: 2.17–6.83; $P<0.0001$). According to recent data, a drastic reduction in exposure to sunlight and to intestinal parasites during childhood, found preferentially among migrants, are possible environmental factors responsible for this emergence.

Keywords: Emergence; Multiple sclerosis; Migration; French West Indies; Neuromyelitis optica; Sun light exposure; Intestinal parasites

1. Introduction

1.1. Multiple sclerosis in the French West Indies in the 1980s

Until the end of the 1980s, inflammatory demyelinating diseases of the central nervous system in the French West Indies (FWI) were represented almost exclusively by myelopathy associated with the HTLV-1 virus [1]. Multiple sclerosis (MS) was rare in the FWI population [2] just as in all Caribbean islands and tropical regions. As in black populations of Sub-Sahara Africa, there were cases of recurrent Devic's neuromyelitis optica (NMO) — at the fringes of the clinical spectrum of MS. During the 1990s, cases of MS were diagnosed in Martinique with increasing frequency [3], raising many questions by neurologists on the origin of these cases in a population previously spared by this disease.

1.2. The French West Indies: two-way migration terrains

The FWI include the islands of Martinique and Guadeloupe that have similar geographic and demographic characteristics of potentially importance for MS epidemiology: humid tropical climate, 40% urbanization, and a young, primarily Afro-Caribbean population, with moderate degree of racial mixing with the Caucasian population (23%). During the 1960s, the two islands underwent the social phenomenon of considerable migration to continental France; this resulted from the combination of demographic growth, restricted local labor markets, and an agricultural crisis affecting the plantations. At the same time, the French industrial economy in full growth after World War II required a large labor force. This led to measures to encourage and facilitate the installation of Caribbean workers in continental France. Following this migratory wave, the first return migration of West Indians to Guadeloupe and Martinique started, very probably favored by increasing unemployment in continental France and the relative economic development of the FWI that abandoned traditional agricultural activities and turned to the industrial sector, in particular tourism. The return first migration was negligible until the end of the 1970s, when it accelerated continuously and more clearly for Martinique than Guadeloupe. In 1999, it represented 36.6% of the population of Martinique and 28.1% for Guadeloupe. The time spent away from the FWI was longer for residents of Martinique than those of Guadeloupe (9.8 years *vs.* 7.2) [4]. The FWI are thus ideal

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Table 1
Prevalence on Dec. 31, 1999 of MS in the French West Indies

	Number	Population at risk	Rate [a] (IC 95%)	Rate [b] (IC 95%)
French West Indies	101	683 000	14.8 (11.9–17.7)	14.1 (11.4–16.8)
Martinique	72	343 000	21.0 (16.1–25.9)	19.6 (14.9–24.3)
Guadeloupe	29	340 000	8.5 (5.4–11.6)	8.8 (5.7–11.9)
Clinical forms				
Martinique: NMO	8	343 000	2.3 (0.6–3.9)	
Martinique: cMS	64	343 000	18.6 (14.0–23.2)	
Guadeloupe: NMO	10	340 000	2.9 (1.1–4.7)	
Guadeloupe: cMS	19	340 000	5.6 (3.1–8.1)	
Migration [c]				
Any age	52	144 000	36.1 (26.3–45.9)	32.1 (22.7–41.5)
No migration	45	297 000	15.1 (10.8–19.4)	14.8 (10.5–19.1)
Migration before age 15	23	24 000	95.8 (56.6–135)	107.2 (52.7–161.7)
Migration after age 15	29	120 000	24.2 (15.4–33)	20.3 (12.7–27.9)

cMS: conventional MS, NMO: recurrent neuromyelitis optica.
[a] Raw rates of prevalence.
[b] Prevalence rates adjusted to the European population.
[c] Population between 15 and 64 years of age on Dec. 31, 1999.

geographic isolates for evaluating the modification of the risk of acquiring MS caused by migration to a temperate zone, all the more so since FWI migrants are genetically representative of the non-migrant source population. The distribution of ABO Rhesus blood groups (indirect parameter of racial mixing) is in fact similar in migrants and non-migrants. Similarly, the extent of racial mixing, based on the analysis of HLA-I allele frequencies, is 24.6% for migrants and 22.9% for non-migrants [4].

A prospective population study of the prevalence and incidence of MS was conducted from January 1, 1998 to December 31, 2004 [4] using the diagnostic criteria of Mc Donald [5] and studying migration as a risk factor for acquiring MS. The originality of the study was the migration of the FWI population to a temperate zone, in contrast with prior studies on migration and MS that mostly involved one-way population migrations along a North–South axis [6–8].

2. Descriptive epidemiology of MS in the French West Indies (4)

2.1. Prevalence

One hundred one cases of MS were prevalent in the FWI population on Dec. 31, 1999, giving a prevalence of 14.8/10^5. The mean age of MS onset was 31.4± 10.7 years and 5.9% were familial forms. Eighteen patients (17.8%) fulfilled the criteria for NMO. The prevalence of MS in Martinique and Guadeloupe was 21.0/10^5 and 8.5/10^5, respectively. The peak of prevalence involved the 35–44 year age-group in Martinique and 25–34 years in Guadeloupe. The sex ratio of MS was 4.1 in Martinique *vs*. 6.2 in Guadeloupe. Conventional MS represented the majority of the clinical forms in Martinique, with 64 cases of conventional MS for 8 cases of NMO, giving respective prevalences of 18.6/10^5 and 2.3/10^5. In Guadeloupe, on the other hand, the proportion of conventional forms of MS was lower, with 19 cases of conventional MS for 10 cases of NMO, with respective prevalences of 5.6/10^5 and 2.9/10^5 (Table 1).

2.2. Incidence

Forty-seven patients presented their first outbreak of MS between July 1, 1997 and June 31, 2002, giving a mean annual incidence of 1.4/10^5 for this period. The mean age of the onset of these incident cases was 34± 11.1 years and concerned 42 women and 5 men. Among these incident cases, 7 were clinically isolated syndromes and one case was the primary progressive form of MS. The respective incidences in Martinique and Guadeloupe were 2.0/10^5 and 0.7/10^5. During this period, there were 4 cases of NMO in Guadeloupe and one in Martinique (Table 2).

2.3. Influence of migration

Sixty-three patients with MS were migrants. The mean duration of residence outside the FWI was 12.5± 9.2 years,

Table 2
Mean annual incidence From July 1997 to June 2002 of MS in the French West Indies

	Number	Population at risk	Rate [a] (IC 95%)	Rate [b] (IC 95%)
French West Indies	47	683 000	1.4 (1.0–1.8)	1.3 (0.9–1.7)
Martinique	35	343 000	2.0 (1.4–2.6)	1.9 (1.2–2.6)
Guadeloupe	12	340 000	0.7 (0.3–1.0)	0.6 (0.3–0.9)
Migration [c]				
Any age	21	144 000	2.9 (1.7–4.1)	2.5 (1.3–3.7)
No migration	25	297 000	1.7 (1.1–2.3)	1.6 (0.9–2.3)
Before age 15	9	24 000	7.5 (2.6–11.9)	6.9 (1.5–12.3)
After age 15	12	120 000	2.0 (0.8–3.2)	1.4 (0.6–2.2)

cMS: conventional MS, NMO: recurrent neuromyelitis optica.
[a] Raw rates of incidence.
[b] Incidence rates adjusted to the European population.
[c] Population between 15 and 64 years of age on Dec. 31, 1999.

Table 3
Standardized prevalence ratios for MS by migration and duration of residence in continental France region prior to onset of disease in the French West Indian population between 15 and 64 years of age on Dec. 31, 1999

	Population at risk	MS-O	MS-E	SPR	95% CI	p
Migration						
Any age	144 000	52	26	1.98	1.48–2.60	<0.0001
Before age 15	24 000	23	3.84	5.99	3.79–8.98	<0.0001
After age 15	120 000	29	22.42	1.29	0.87–1.86	0.20
Duration of migration (years)						
<5 years	57 000	11	9.89	1.11	0.55–1.99	0.95
5–10 years	39 000	14	7.67	1.83	0.99–3.04	0.06
>10 years	48 000	27	8.71	3.10	2.01–4.47	<0.0001

MS-O: MS cases observed. MS-E: MS cases expected deriving from age-specific prevalence of MS in non-migrants.

mostly in the Paris region (82.5%). The prevalence of MS in the population between 15 and 64 years of age on Dec. 31, 1999 was higher among migrants ($36.1/10^5$) compared to non-migrants ($15.1/10^5$). Migration to CF before the age of 15 multiplied the risk of MS five-fold compared to a migration after the age of 15 (Table 1). The mean annual incidence of MS for the study period was $2.9/10^5$ among migrants *vs*. $1.7/10^5$ among non-migrants. Similarly, residence in CF before the age of 15 years increased the incidence rate compared to a residence that started after this age: $7.5/10^5$ *vs.* $2.0/10^5$ (Table 2). Tables 3 and 4 show the standardized ratios of prevalence and incidence of MS among West Indian migrants.

3. Comments

3.1. The reality of MS emergence

The prevalence of MS on Dec. 31, 1999 shows that the FWI are now within the scope of moderate prevalence. In spite of the absence of prior epidemiological studies, several arguments plead in for the recent emergent character of MS in the FWI. MS had long been tracked by neurologists in the FWI since it was a differential diagnosis of myelopathy associated with the HTLV-1 virus, endemic in the islands. Its extreme rarity in the 1980s was thus not due to a lack of diagnosis or understanding of the disease. In Martinique, the peak of prevalence of MS is in the 35–44 year category, followed by an unusual drop in the 45–54 year age-group. Similarly, the peak of prevalence in the population of Guadeloupe, unusually early in the 25–34 year group, reflects an even more recent emergence of MS, in agreement with an overall lower prevalence than that observed in Martinique.

The conventional form of MS in the FWI currently represents the majority of cases, compared to NMO whose prevalence remains low even if its rate in the FWI is slightly higher than that observed in Southeast Asia [9] where it ranges between $0.27/10^5$ and $0.74/10^5$. The F/M sex ratio of MS in Martinique is high but lower than that of Guadeloupe, where the prevalence of MS in men remains low. Even though the disease classification of NMO is a topic of discussion [10], these data support the conclusions of Japanese authors according to whom NMO could be a primary form of MS whose prevalence increases with the appearance of masculine cases resulting in a progressive drop of the F/M sex ratio. The emergence of MS in the FWI is also shown by a high mean annual incidence in Martinique, where the rate of $2.0/10^5$ gives it a practically epidemic aspect.

3.2. The emergence of MS is environmental

The prevalence of MS is higher among migrants than non-migrants, more so if residence in continental France started before the age of 15 years. Studies of migration from a zone of high prevalence to zones of low prevalence in Caucasian populations suggest that the risk of acquiring MS is indeed determined before 15 years of age [6.7]. Studies evaluating the role of migration in the occurrence of MS in black populations are limited to immigrants in the United Kingdom from the Caribbean: the prevalence of MS among children born of migrants to the United Kingdom is similar to that of the white population [11] whereas migrants increase their risk of MS with no notable effect of age at which the migration occurred [12]. In Martinique, migration was longer and its amplitude higher than in Guadeloupe. Since continental France is in a region of high prevalence of MS [13], the higher rates of prevalence and incidence in Martinique compared to Guadeloupe are factors that favor the role of return migration in the emergence of MS in the FWI.

3.3. What environmental factors?

Return migration could have been the vector of introduction in the FWI of known or still unknown infectious environmental factors, operating in the acquisition of MS preferentially before the age of 15. Migrants initially bearing the transmissible factors acquired in continental France would have secondarily enabled the emergence of MS in the non-migrant population by contamination. This scenario would thus mimic the model of the Faroe islands, where the first MS epidemic was observed in a disease-free insular

Table 4
Standardized incidence ratios for MS by age at migration to continental France prior to onset of disease in the French West Indian population between 15 and 64 years of age on Dec. 31, 1999

	Population at risk	MS-O	MS-E	SIR	95% CI	p
Any age	144 000	33	19.3	1.71	1.19–2.38	<0.01
Before age 15	24 000	14	3.46	4.05	2.17–6.83	<0.0001
Between 15 and 20	48 000	10	6.85	1.46	0.52–2.71	0.28
After age 20	72 000	9	9.0	1.0	0.45–1.87	0.95

MS-O: MS cases observed. MS-E: MS cases expected deriving from age specific mean annual incidence of MS in non-migrants for the period 01/01/1995–12/31/2004.

population following contact with English occupation forces during the World War II [14].

Alternatively, local environmental upheavals, whether socio-economic or health-related, should be considered as in Sardinia, where the repeated measurement of the incidence of MS showed its concomitant appearance with its rapid westernization after the war [15]. These local environmental modifications would also explain the current overrepresentation of conventional forms of MS compared to NMO. In Japan, it has been shown that there was a progressive reduction in the NMO/conventional MS ratio according to the decade of birth of Japanese subjects afflicted with MS, in parallel to the economic growth of the country [16].

These environmental modifications could be protective. The recent and progressive disappearance of factors exerting their protective effect essentially before the age of 15 in the FWI could explain the emergence of MS in the non-migrant population, *a fortiori* since the migrant population was completely spared from these protective factors by migration. This is consistent with the recent underexposure of the FWI population to environmental factors that could prevent MS and having affected primarily migrants. This novel concept of protective factors can be substantiated at three levels: ecological, experimental and case-control studies (Table 5). Ecological data render the solar protection hypothesis plausible and could explain the well known gradient of MS prevalence observed in the two hemispheres closely related to increasing level of exposure to sunlight from the poles to the Equator. Experimentally, repeated UVB irradiation in a model of MS not only reduced its frequency of occurrence but has also modified its immunopathologic spectrum by producing a sub-type rich in the production of antibodies to myelin [17]. Finally, a recent case-control study conducted in Martinique, Cuba and Sicily also argues in favor of solar protection since mean reduction of exposure to sunlight, protection from the sun and the absence of practicing water sports during vacations (OR 4.35, 95% CI 2.6–7.7, $P<0.0001$) were independently correlated with a high risk of MS [18]. In the FWI, reduced solar exposure of young generations, related to recent phenomena of urbanization, the relative abandon of traditional habitat, and the progressive shift from agricultural life to service industries support this hypothesis.

Table 5
Possible environmental factors protecting against MS

Protective factors	Ecological data	Experimental data	Case-control studies
Sunlight: UVB	+++ North–South gradient MS	+ SJL/J mice (MOG)	++ Martinique, Cuba Sicily
Helminthiases: *S. mansoni*	++ "Mirror images" MS-Helminthiases French West Indies	++ SJL/J mice (PLP) C57BL/SJ mice (MOG)	?

For several decades, it was suggested that MS resulted from an infectious aggression during childhood or in the teenager years. Nevertheless, its incidence has not been reduced by large scale vaccinations against viral infections and the reduction in common bacterial infections in countries with highly developed health care systems [19]. In several geographic isolates, and even in Mediterranean islands, it has been observed that an increase in MS incidence can be related to a parallel increase in incidence of other organ-specific auto-immune diseases such as insulin-dependant diabetes mellitus and inflammatory enteropathies. In addition, the increased incidence of MS in the FWI is accompanied by the recent emergence of ulcerative colitis and Crohn's disease [20]. These ecological data are now turning towards the hygienic hypothesis of MS. Concerning parasites, it is undeniable that childhood and teenage MS and helminthes diseases present a "mirror image" of their epidemiology. In addition, two recent publications are noteworthy. The first involved preventing MS in a murine model induced by a myelin PLP (proteolipid protein) epitope by infecting animals with the eggs of *Schistosoma mansoni*. The authors also showed that the protective mechanism resulted from a type Th1 immunodeviation to Th2 induced by the parasite, with MS in its archetype being considered as a model of auto-immune disease with a type Th1 response [21]. The second confirmed the protective effect of *S. mansoni* eggs in another murine model induced by the 35–55 myelin epitope of MOG (myelin oligodendrocyte glycoprotein) [22]. Until quite recently, the FWI were an endemic area for multiple intestinal parasitism in children younger than 15 years, with the leading disease being schistosomiasis [23] whose eradication has been demonstrated by several epidemiological population studies resulting from a specific anti-vector campaign. Furthermore, the hypothesis of protection by helminthes via a type Th2 immunodeviation could also explain the inversion of the spectrum of nervous system demyelinating diseases in the FWI, with a quantitative reduction in NMO following a humoral type immune mechanism in favor of more conventional forms of MS that follow a cell-mediated immune mechanism. Nevertheless, it still remains necessary to conduct difficult case-control studies in this area using relevant tools of exposure to the risk by eliminating all ambiguous factors.

4. Summary

The FWI are now on the list of geographic isolates where MS is emergent. They are nevertheless distinguished by their geography and population as an area where MS could be dogmatically considered as "highly improbable". They are also the illustration of a disease long reduced to its borderline form, NMO, which then enlarged its clinical spectrum. Recent migratory movements render FWI an ideal study situation to test novel hypotheses such as protective factors against this still mysterious disease.

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