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Clinical features and disability progression in multiple sclerosis in Tunisia: Do we really have a more aggressive disease course?

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ABSTRACT

Background: Few epidemiological data are available on multiple sclerosis (MS) patients in North Africa (NA). Studies of immigrants from NA showed a more aggressive course compared to European patients.
Objective: The aim of this study is to describe clinical and long term course characteristics of MS in Tunisia and to compare it to European cohorts.
Method: A total of 437 MS patients from three hospital based cohorts in Tunisia and having prospective follow up between 2010 and 2012 were analyzed. We considered as endpoints the time to reach EDSS scores of 3, 4 and 6 in the different clinical forms of MS and the beginning of a secondary progressive (SP) phase.
Results: Sex ratio was 2.34. Mean age of onset was 30.3 years. The course was relapsing–remitting (RR) in 91% of patients and primary progressive (PP) in 9%. The most frequent isolated onset symptoms were respectively motor (28%), optic neuritis (20%) and sensory (16%) dysfunction. Median time to SP onset was 19.1 years. Median times from onset of multiple sclerosis to assignment of a score of 3, 4 and 6 were 8, 10.7 and 15 years respectively. Benign form of MS represented 31.5%. Median interval from the onset of the disease to EDSS score of 3, 4 and 6 was shorter in PP-MS than in RR-MS. However, there was no difference between these two groups for the median time from the assignment of EDSS 4 to the assignment EDSS 6.
Conclusions: Our study shows that Tunisian MS patients have a quite similar clinical feature to European patients. Still, larger MS multicenter cohort studies in NA with longer follow-up duration could clearly respond to the issue.

1. Introduction

Multiple sclerosis (MS) is the most frequent chronic, disabling neurological disease in young adults [1]. It affects 1 to 1000 people in western countries [2]. MS is less frequently found in North African (NA) than in European individuals [3,4]. NA countries are considered as a low to medium prevalence zone [5,6]. Genetic predisposition, unknown environmental factors, or a combination of both may explain the variable prevalence of MS in the world [7–9]. Although few epidemiological data are available concerning MS patients in NA, studies of immigrants from NA showed a more aggressive course of MS in NA than in European patients [10,11].

In this study, we aimed to describe the clinical and laboratory characteristics of MS in a Tunisian multicentric cohort, its course and prognosis and to compare the natural history of MS in our NA population to European patients.

2. Methods

2.1. Patient sampling and data collection

Patients were identified through three hospital based cohorts: Razi hospital cohort in Mannouba, Military hospital cohort in Tunis and Habib Bourguiba hospital cohort in Sfax. The latter is located in the southern part of the country whereas the two others are located in the northern part. They represent major referral centers for in- and outpatients in Tunisia.

We conducted a two-step study: in step 1 from 1988 to 2010, we obtained data retrospectively from the primary medical files on the first neurological episode, the clinical course and disability, in addition to cerebrospinal fluid (CSF) and MRI data; in step 2 from 2010 to 2012, we prospectively recorded data after each visit to a neurologist in a common Database and the new data were checked for consistency with previous information by neurologists in charge of the study.

Individual case reports included the following data: identification and demographic data; medical history; key episodes in the course of MS including date of disease onset, date of diagnosis, relapses, onset of

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the progressive course, Expanded Disability Status Scale (EDSS) score [12], times of assignment of the successive scores of irreversible disability, biological, MRI data and treatment. Progression index was calculated for each individual by dividing the EDSS score at last follow-up with disease duration (years) [13].

2.2. Definition of cases and assessment of patients

By December 2012, we included 437 patients in the database.

Inclusion criteria were cases with a definite MS diagnosis. Diagnosis of MS was established according to McDonald's criteria revised in 2005 [14]. Since revision of McDonald's criteria in 2010 [15], all cases of probable MS were re-examined according to this classification.

Exclusion criteria were patients presenting with Devic disease, lupus, sarcoidosis, Sjogren syndrome, or Behcet disease.

A relapse of MS was defined as the occurrence, recurrence or worsening of symptoms of neurological dysfunction lasting >24 h and usually ending with a remission, which is either partial or complete. Fatigue alone and transient fever-related worsening of symptoms were not considered as a relapse. Symptoms occurring within 1 month after the initial symptoms of relapse were considered to be part of the same episode. The progressive phase was defined as the steady worsening of symptoms and signs for at least 1 year, whether superimposed with relapses or not [14]. Once started, it goes on continuously throughout the disease, although occasional plateaus and temporary minor improvements may be observed [16]. Overall course was classified relapsing–remitting when the disease exhibited only relapses and remissions; secondary progressive when an initial relapsing–remitting phase was followed by a progressive phase; and progressive from onset when the progressive phase took place right from disease onset. Benign MS corresponded to EDSS score ≤3 after 10 years from disease onset.

A series of clinical variables that can be determined at the clinical onset of MS were systematically assessed for each patient. They included gender and age at onset of MS. Initial symptoms were categorized into isolated optic neuritis, isolated brainstem dysfunction (including bulbar function, eye movements and vertigo), isolated dysfunction of long tracts (including motor, sensory and cerebellar dysfunction) and combination of these symptoms. Initial course of the disease was classified as relapsing–remitting or progressive.

To determine the extent of neurologic disability, the EDSS score (range 0 to 10) was recorded during each visit of the patient to the neurologist. Disability was defined as irreversible when the assignment of a given score persisted for at least 6 months, thus excluding any transient worsening of disability related to relapses. By definition, when a given score of irreversible disability had been assigned to a given patient, all the scores of disability that could be subsequently assessed during the follow-up were either equal to or higher than that one. For each patient, the date of assignment to a given score of irreversible disability was assessed whenever appropriate.

Recovery from the first relapse was classified as incomplete (persistence of neurological signs, corresponding to an EDSS score of at least 2) or complete (absence of neurological signs, corresponding to an EDSS score of 0 or 1). The date of onset of the second neurological episode of MS, which may be a relapse or the onset of the progressive phase, was also systematically determined whenever appropriate.

Oligoclonal immunoglobulin G (IgG) bands (OCB) were assessed using isoelectric focusing (IEF) and immunofixation (Hydragel CSF isofocusing, Hydrasys-Sebia).

2.3. Statistical analysis

Categorical and continuous variables were compared using the X^2 test and Student *t*-test. We estimated survival according to the Kaplan–Meier method and the log-rank test was used for univariate analyses. The end point was the time to irreversible disability, as indicated by a score of 3, 4, or 6 on the EDSS. Data on patients who had not reached an end point were censored at the time of the last clinic visit. Differences were considered significant at $P < 0.05$. All computations were performed with the use of SPSS software for Windows (version 18.0).

Table 1
Baseline demographic and disease-related characteristics of patients.

Characteristics	Value ($n = 437$)
Gender, *n* (%)	
Male	131 (30%)
Female	306 (70%)
Age of onset of MS (years)	
Mean ± SD	30.3 ± 9.5
Range	4–60
Distribution, *n* (%)	
0–19	50 (11)
20–29	178 (41)
30–39	136 (31)
40–49	61 (14)
≥50	12 (3)
Initial symptoms, *n* (%)	
Isolated optic neuritis	87 (20)
Isolated brain-stem dysfunction	15 (4)
Isolated dysfunction of long tracts	198 (45)
Motor	122 (28)
Sensory	69 (16)
Cerebellar	7 (2)
Combination of symptoms	137 (31)
Initial course of MS, *n* (%)	
Relapsing–remitting	400 (91)
Progressive	37 (9)
Time from onset of disease to initial clinic visit (years)	
Mean	2.8 ± 4.7
Range	0–37
Time from onset of disease to MS diagnosis (years)	
Mean	3.4 ± 4.9
Range	0–40
Kaplan–Meier estimate of time from onset of disease to second neurologic episode (years)	
Mean	2.2 ± 2,8
Median	1
Range	0–20

3. Results

3.1. Characteristics and initial course of the patients with MS

The baseline characteristics of 437 patients with a definite diagnosis of MS are given in Table 1. The mean duration of follow-up was 8.5 ± 6 years. Concerning the dropout rate, it appeared that we had no recent exam for 87 patients (20%) during the last three years and only for 28 patients (6.4%) during the last eight years. The mean visit frequency was 3.8 ± 2 visits/year and the median was 4 visits/year. There were 131 males and 306 females (ratio 1:2.34). Mean age of onset was 30.3 ± 9.5 years; this was slightly higher in males (31.25 years) than

Table 2
Kaplan–Meier estimate of median time to the onset of irreversible disability and to the secondary progressive form.

	Number of patients	Median time (years) [95% CI]	Patients who did not reach the end point (%)
Time from MS onset to assignment of EDSS 3	437	8 [6.8–9.1]	50
Time from MS onset to assignment of EDSS 4	437	10.7 [9.4–12]	59
Time from MS onset to assignment of EDSS 6	437	15 [12.6–17.4]	73
Time from MS onset to the secondary progressive form	400	19.1 [16.3–21.9]	84