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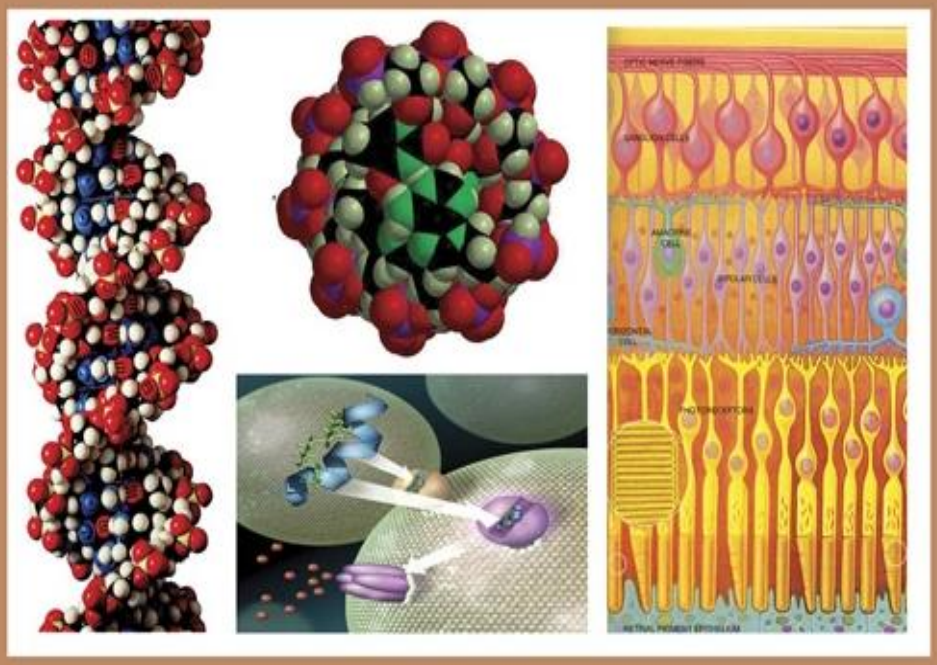

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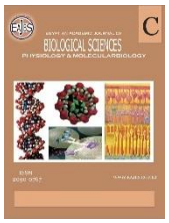

Clinical and Epidemiological Characteristics of Multiple Sclerosis MS and The Association Between Familial MS and Consanguinity in The Region of Tlemcen (Western Algeria)

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ABSTRACT

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, of immune origin. The aim of this work was to study the epidemiology and clinical parameters of MS patients and to establish the association between familial MS and consanguinity. A retrospective study was conducted on the medical records of 129 patients with MS diagnosed at the Neurology department of the Tlemcen UHC, in order to determine the epidemiological profile and the biological characteristics. The period is between June 2019 and May 2021. Our sample was reported with 103 women and 26 men, a percentage of 79.8% and 20.2% respectively. The sex ratio (female/male) was 3.96. The patient's minimum age was 19 and 72 years old with a mean of 40.41 ± 11.72. The mean age of disease onset was 30.71 ± 11.30. The association between consanguinity and familial MS was not significant p = 0.141. The EDSS scale (Expanded Disability Status Scale) was between 0 and 6, with a mean of 2.32 ± 1.42. Among the MS forms, there is a predominance of the relapsing-remitting form (76%), secondary progressive (21.7%) and primary progressive at 2.3%. No significant association was observed between gender and clinical evolution p = 0.432. A significant association between the clinical evolution of MS and the EDSS p=0.000. The MS increased prevalence in the Tlemcen region is probably due to cultural factors. The association with consanguinity was not significant, but the hypothesis is not discarded.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease whose etiopathology remains unknown, although it is widely accepted that the disease onset results from the interactions of genetic and environmental factors (Lopetegi *et al.*, 2019). The presence of disseminated demyelinating lesions in the central nervous system (CNS) and the association with autoimmunity characterize this chronic pathology. Potentially autoimmune, the activated T cells cross the blood-brain barrier and produce inflammatory plaques and axonal loss in the spinal cord, brain, or optic nerves. Demyelination and gliosis accumulation in CNS regions is the end result (Rodrigo *et al.*, 2011).

More than 2.5 million individuals are affected worldwide, and there is evidence of increasing incidence (Alonso and Hernan, 2008). especially among women, with a clear increase in the female/male sex ratio (Orton *et al.*, 2006). A very high prevalence has been described in North America and Europe, while a lower prevalence is reported in East Asia and sub-Saharan Africa (Leray et *al*., 2016). North Africa has transitioned from a low-prevalence region to a medium to high prevalence in about 40 years (Browne *et al.*, 2014; Leray *et al*., 2016). In many Middle Eastern and North African (MENA) countries; the prevalence and incidence of MS are not well documented, including in Algeria, and most prevalence estimates are from isolated hospital studies. (Heydarpour *et al.*, 2015). The MS prevalence in Algeria was 10 per 100,000 in 1984 (Boukhelifa Chaouch, 1984), in 2016, in the Blida municipality (central Algeria) it was 39.7 per 100,000 inhabitants (Drai, 2018), and then 41.5 per 100,000 inhabitants in the Tlemcen municipality on May 2018 (Bedrane *et al.*, 2019).

The prevalence and severity of multiple sclerosis are mainly determined by ethnic factors (Araqi-Houssaini *et al.*, 2014). North Africans born or raised in a country with a high prevalence of MS are vulnerable to developing the disease. The objective of our study was to describe the clinical and socio-demographic characteristics of MS patients treated at the medical neurology department of the Tlemcen University Hospital, to perform a comparative study between the sexes, also to compare clinically the MS forms and the association determination between familial MS and consanguinity in these patients.

MATERIALS AND METHODS

Population:

The study was conducted in the neurology department of the Tlemcen university hospital (Western Algeria) from June 2019 to May 2021. After completing a questionnaire and reviewing the medical records, 129 MS patients with the McDonald criteria 2017 were identified. After magnetic resonance imaging (MRI) exploration, some patients had demyelinating lesions in the brain, others in the spinal cord, and some had lesions in the brain and spinal cord at the same time. The majority of patients were subjected to lumbar puncture (LP) for the cerebrospinal fluid (CSF) immunological study.

The Statistical Analysis:

The data statistical analysis was performed by SPSS 22.0 (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL. August 2013). Qualitative variables were expressed in percentage and frequency, and the quantities one was presented as mean with standard deviation (SD).

The Pearson chi-square test ($\chi 2$) and the ANOVA test were used for comparison. The significance level was at the p-value $\leq$ 5%. Ethics: The study was approved by the medical committee of the university hospital of Tlemcen and the department of Biology, Djillali Liabes University.Pearson's chi-square test ($\chi 2$) and ANOVA test were used for comparison. The significance level was at the p-value $\leq$ 5%. Ethics: The study was approved by the medical committee of the UHC of Tlemcen and the biology department of Djillali Liabes University.

RESULTS

In total, 103 women were registered and 26 men with a rate of 79.8% and 20.2% respectively with a female/male sex ratio of 3.96.

The patients' minimum age was 19 years old and the maximum was 72 years old with a mean of 40.41 ± 11.72. The most affected age group is [39-49] years old, with a frequency of 45 years (35.4%), of which (37.6%) were women (Table 1). On the other hand, the majority of male patients (34.6%) belonged to the age group of 29 to 39 years old, and 38 patients lived in rural areas (Table 1). A consanguinity notion was noted, it was estimated at 24% (31 patients), and 22 patients had a family history of MS with a rate of 17.1%, the association between consanguinity and familial MS is illustrated in

Figure 1, which was not significant with a p-value of 0.141. Regarding the blood group, the patients' majority (57) were O rhesus positive, the proportions of each blood group are shown in Figure 2.

For BMI, the mean was 23.32 ± 2, 99, with a minimum of 17 and a maximum of 38. the mean age of disease onset ranging from 11 to 64 years old was 30.71 ± 11.30. Thus, in the affected individual's majority, the disease appears between the ages of 20 and 30 years old, in both sexes (Table 2). The mean age at diagnosis was 32.14 ± 8.34. On average, patients were diagnosed 2 years after the first appeared symptoms. The patients' EDSS was between 0 and 6 with a mean of 2.32 ± 1.42, most had an EDSS between 1.5 and 2.5 (Table 2). The most frequent form in our series was a relapsing-remitting MS with a rate of 76%, 21.7% had a progressive secondary evolution and 2.3% had a progressive primary MS. No significant association was observed between gender and clinical evolution p = 0.432 (Table 2).

We compared the three clinical phenotypes of MS, there was a significant association between the clinical evolution of MS and the EDSS p = 0.000. In fact, for primary progressive MS, the mean EDSS was 6, it was estimated at 4 for the secondary-progressive evolution and at 1.7 for the relapsing-remitting evolution. No significant correlation was observed with the other parameters (Table 3).

Among the most frequent symptoms in MS patients, visual disorders were estimated at 45.7% (n=59), including diplopia, which is a diagnostic criteria in MS, weakness, motricity symptoms, tiredness, myalgias, electrical discharge, disequilibrium, vertigo, tingling and numbness, while there are other less frequent symptoms such as auditory disturbance, ataxia, dysarthria, dysphagia, dystonia and headaches (Table 4).

Some patients had associated diseases with MS, including diabetes with a percentage of 4.7%, thyroid problems at 7.0%, high blood pressure at 13.2%, and epilepsy at 5.4%. Among the patients' family history, we also found diabetes with a high frequency of 80 (62%), 40 had a family history of thyroid disease (31%), 80 of high blood pressure (62 %), 20 of cancers (15.5 %), 28 of cardiac diseases (21.7 %), 20 of stroke (15.5 %), asthma with a frequency of 14 (10.9 %) and neurodegenerative diseases particularly Parkinson's (1.6 %) and Alzheimer's (4.7%).

Table 1: Clinical and socio-demographic characteristics of the study population.

Total number of patients	N=129
Mean age (years old) [a]	40.41 ± 11.72 (19-7)
Male [b]	26 (20.2 %)
Female [b]	103 (79.8 %)
Sex ratio (female/male)	3.96
Rural Area [b]	38 (29.5 %)
Consanguinity [b]	31 (24 %)
Family history of MS [b]	22 (17.1 %)
BMI [a]	23.32 ± 2.99 (17-38)
Age at onset [a]	30.71 ± 11.30 (11-64)
Age at diagnosis [a]	32.14 ± 8.34 (11-63)
Time between MS onset and diagnosis [a]	2.02 ± 2.88
EDSS [a]	2.32 ± 1.42 (0 - 6)
Clinical phenotype	
PPMS [b]	3 (2.3 %)
SPMS [b]	28 (21.7 %)
RRMS [b]	98 (76 %)

[a] Expressed with mean ± standard deviation

[b] Expressed with number and %.

BMI (Body Mass Index)
PPMS (Primary progressive multiple sclerosis)
SPMS (Secondary progressive multiple sclerosis)
RRMS (Relapsing-remitting multiple sclerosis)

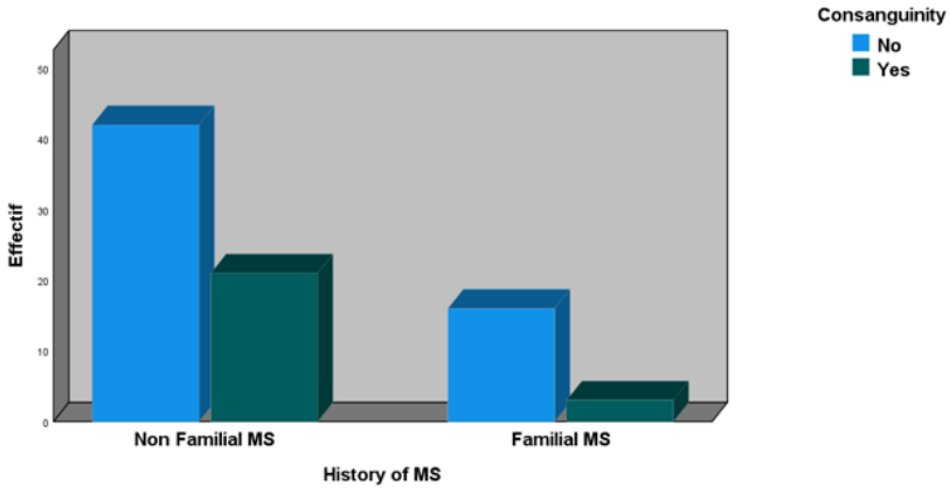

Fig.1: Association between consanguinity and family history of MS.

Table 2: Association gender by age, age at onset MS, EDSS and Clinical Phenotype.

	Female	Male	Total	P-value*
Age				
[19-29[	20 (19.8 %)	3 (11.5 %)	23 (18.1 %)	0.362
[29-39[	22 (21.8 %)	9 (34.6 %)	31 (24.4 %)	
[39-49[	38 (37.6 %)	7 (26.9 %)	45 (35.4 %)	
50 and more	21 (20.8 %)	7 (26.9 %)	28 (22 %)	
Age at onset MS				
[11-20[	16 (16.5 %)	5 (19.2 %)	21 (17.1 %)	0.628
[20-30[	31 (32 %)	11 (42.3 %)	42 (34.1 %)	
[30-40[	30 (30.9 %)	5 (19.2 %)	35 (28.6 %)	
40 and more	20 (20.6 %)	5 (19.2 %)	25 (20.3 %)	
EDSS				
[0-1.5[	21 (20.4 %)	5 (19.2 %)	26 (20.2 %)	0.271
[1.5-2.5[	46 (44.7 %)	12 (46.2 %)	58 (45 %)	
[2.5-4.5[	19 (18.4 %)	8 (30.8 %)	27 (20.9 %)	
[4.5-6]	17 (16.5 %)	1 (3.8 %)	18 (14 %)	
Clinical Phenotype				
PPMS	3 (2.9 %)	0 (0.0 %)	3 (2.3 %)	0.432
SPMS	24 (23.3 %)	4 (15.4 %)	28 (21.7 %)	
RRMS	76 (73.8 %)	22 (84.6 %)	98 (76 %)	

*Data analyzed by Pearson chi-square test ($\chi 2$). Values presented as Number (%).

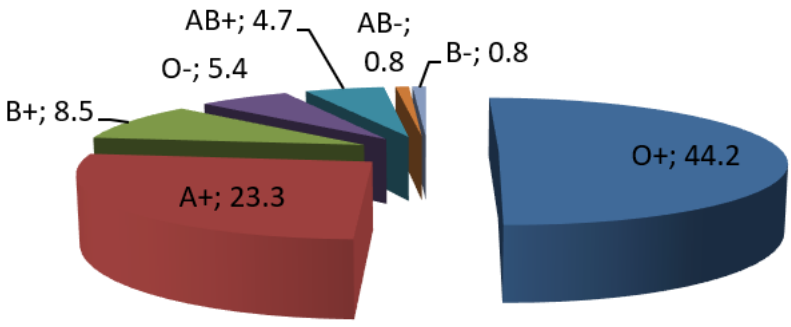

Fig. 2: Population distribution by blood type.

Table 3: Comparative demographic and disease-related characteristics of primary progressive secondary progressive and relapsing-remitting cases.

	Primary-progressive multiple sclerosis n=3	Secondary progressive multiple sclerosis n=28	Relapsing-remitting multiple sclerosis n=98	P-value
Females [a]	3 (2.9 %)	24 (23.3 %)	76 (73.8 %)	
Mean age [b]	44 ± 1	43 ± 9.2	39.5 ± 12.5	0.354
Age at MS onset (years) [b]	34 [32-35]	30 [19-51]	30 [11-64]	0.857
Age at MS diagnosis (years) [b]	34 ± 1.7	33 ± 9.7	31 ± 11.1	0.811
EDSS [b]	6 [6-6]	4 [2-6]	1.7 [0-5]	0.000
BMI [b]	22.67 ± 2	22.85 ± 3.4	23.67 ± 4.6	0.749

[a] Pearson chi-square test ($\chi 2$). Values presented as a number (%).
[b] ANOVA test. Values presented as a mean ± standard deviation.

Table 4: Disease-related symptoms.

-Most common symptoms		
Visual disturbances	59 (45.7 %)	whose diplopia 22 (17.1 %), visual disorders 32 (24.8 %)
Back pain	44 (34.1 %)	
Weakness	66 (51.2 %)	
Motricity symptoms	65 (50.4 %)	
Tiredness	77 (59.7 %)	
Cramps	40 (31.0 %)	
Myalgias	48 (37.2 %)	
Electrical discharge	39 (30.2 %)	
Brain stem symptoms:		
Imbalance	60 (46.5 %)	
Dizziness	46 (35.7 %)	
Numbness	37 (28.7 %)	
Urinary system dysfunction	48 (37.2 %)	
Sexual dysfunction	13 (10.1 %)	
Paresthesia:		
Tingling	74 (57.4 %)	
Numbness	67 (51.9 %)	
Itching	31 (24.0 %)	
Cerebral signs:		
Tremor	33 (25.6 %)	
Memory impairment	17 (13.2 %)	
-Less common symptoms		
Auditory disorders	5 (3.9 %)	
Cerebral signs:		
Ataxia	14 (10.9 %)	
Brain stem symptoms:		
Dysarthria	24 (18.6 %)	
Dysphagia	17 (13.2 %)	
Dystonia	28 (21.7 %)	
Headaches	51 (39.5 %)	

Values presented as a number (%).

DISCUSSION

Multiple sclerosis was a rare and little-studied disease in North Africa, particularly in Algeria. On the other hand, its prevalence in this region has significantly increased in recent years, which justifies our investigation. In our study, the sex ratio (woman/man) was 3.96. Women are more frequently affected than men in most autoimmune diseases (Beeson, 1994). Environmental, hormonal, sexual, or even genetic factors could be attributed to this predominance (Milo and Kahana, 2010; Sellner *et al.*, 2011). It was noted that the patients' majority lived in urban areas. There are potential risk factors for MS development associated with urbanization, including reduced sun exposure, higher body weight, increased stress and smoking (Mouhieddine *et al.*, 2015). In our group, the patients had a mean BMI that was in the normal weight range and this did not influence the MS clinical evolution (Tables 1 and 3). According to our data, the patients 'majority were of blood types O+, A+ and B+. According to the study by Lopetegi *et al* in the Netherlands, the

presence of Rh+ A or B seems to be a risk in multiple sclerosis development, while the immune antigens absence (A, B or Rhesus +) defined by the O-group seems to be protective in the MS group with a probability ratio of 0.49 (95% confidence interval 0.309–0.796). In addition, further functional studies are required to examine the significance of this association and the functional implications. The mean age of MS onset in our population was 30.71 years old, whereas that diagnosis was 32.14-year-old, s. According to Finlayson, most individuals are diagnosed with MS between the ages of 20 and 50 old (Finlayson, 2004) and, until advanced age, more than 30% of this subgroup remain in relapsing-remitting multiple sclerosis (RRMS) (Scalfari *et al.*, 2014; Tutuncu *et al.*, 2013). Some people, however, are diagnosed after the age of 50 (referred to as late-onset MS "LOMS") or even after the age of 60 (referred to as very late-onset MS "VLOMS").

The period between the disease onset and the diagnosis moment time seems to be shorter in recent years in the Maghreb countries, especially in Algeria, it is 2.02 ± 2.88 in our investigation, whereas it is 3.4 ± 4.9 years old (Sidhom *et al.*, 2014), 3.2 years old (Bedrane-Barka, 2012), 3.70 ± 4.90 years old (Drai, 2018) and 2.9 years old (Bouali *et al.*, 2020). A large number of familial MS and patients from consanguineous marriages were found but the association between these two parameters was not significant (Fig 1), which provides further indication that multiple sclerosis is not a hereditary disease, but related to genetic factors, a lower rate of family forms (2.4%) was reported by an old Algerian study (Boukhelifa Chaouch, 1984), another Algerian study found 14.2% of cases with a MS family history (Barka Bedrane *et al.*, 2018), in our study, 17.1%. 20% of MS cases may be familial, although most occur sporadically (Carton *et al.*,1997; Kahana, 2000). Patients with multiple sclerosis clinically present with a panoply of neurological signs and symptoms associated with temporally disseminated white matter lesions in time and space, which either manifest suddenly or are insidious and progressive. (Milo and Kahana, 2010).

In our group, the patients presented frequent disorders as well as less frequent disorders as found in the literature. Paresthesias or numbness, monocular visual disturbances (optic neuritis), motor weakness, diplopia, incoordination, dizziness and vertigo are the most common clinical manifestations (Milo and Kahana, 2010). In recent years, researchers have identified the high prevalence of comorbidity in the MS population in recent years (Marrie *et al.*, 2015). In our study, there were patients with concomitant diseases or in the family environment.

The clinical pattern of multiple sclerosis is highly variable: relapsing-remitting form (RR-MS) is initially presented by almost 85% of patients, and it is characterized by intense relapses of new or recurrent neurological disorders and symptoms, followed by or a remission, lasting from a few days to several months, separated by variable periods of the neurological state stability without a disease clinical activity. A primary progressive form (PPMS), which is distinguished from the disease onset by a regular accumulation of neurological disorders (mainly progressive myelopathies) is presented by approximately 10 to 15% of patients. Some of them have superposed relapses, known as progressive-relapsing MS (PRMS). An increasing subject with RRMS progress over time to a secondarily progressive form (SPMS), where the neurological handicap disability progressively accumulates with or without a new relapse (Compston, 2006).

In our study, the patients' majority had the relapsing-remitting form, followed by the secondary progressive form and a reduced percentage of the primary progressive form, no patient had the progressive-relapsing form. We compared these three MS forms and we noticed that neither the onset age nor that of diagnosis have any influence on the disease form, but there was a strong association between the EDSS and the clinical phenotype. We distinguish the primary progressive form

severity with the highest mean EDSS, succeeded by the secondary progressive form with a mean EDSS evaluated at 4 and a mean EDSS of 1.7 for the relapsing-remitting type (Table 3), this is consistent with a study conducted on a Moroccan population (Ait Ben Haddou *et al.*, 2014). The MS phenotype in North African patients is more severe, according to data from other studies (Algerian, Moroccan and Tunisian) (Araqi-Houssaini *et al*., 2014; Hecham *et al.*, 2014; Sidhom *et al.*, 2017).

Conclusion

The Tlemcen region is classified as a high-risk area due to the increase in MS prevalence. This increase in prevalence is probably due to cultural and socio-economic changes in this population, also the availability of earlier diagnostic methods. But above all the consanguinity factor, although in our series the association was not significant, it remains a study line, considering the high frequency of family MS and the high rate of consanguineal marriage in the Tlemcen region. Possibly with a larger population, the association between disease and consanguinity appears stronger. It is, therefore, necessary to continue the molecular research with a larger sample in order to prove our hypothesis and thus better prevent the disease.

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Conflict of interest: The authors declare no conflicts of interest.

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