American Journal of Epidemiology and Infectious Disease, 2016, Vol. 4, No. 1, 1-9
Available online at http://pubs.sciepub.com/ajeid/4/1/1

DOI:10.12691/ajeid-4-1-1

Multiple Sclerosis in Cyprus: A Fourteen Year (2000-2014) Epidemiological Study

Elena Charalambidou[1], Marios Pantzaris[2], Ioannis Patrikios[2,3,*]

[1]European University Cyprus, Department of Health and Science Nicosia, Cyprus
[2]The Cyprus Institute of Neurology and Genetics, Clinic C, Nicosia, Cyprus
[3]European University Cyprus, School of Medicine, Nicosia, Cyprus
*Corresponding author: i.patrikios@euc.ac.cy

Abstract **Background**: Multiple Sclerosis (MS) is a complex, multifactorial, chronic disease resulting from the interplay between two major factors, environmental and genetic. Cyprus is one of the countries without real history on epidemiological information for the disease and without any records based on scientific evidence. **Methods**: The present study is a descriptive as well as a comparative study. We analyzed retrospectively the records of the MS patients admitted to the Cyprus Institute of Neurology and Genetics (CING), between the years 2000-2014. A total of 427 MS patients were studied that is the 25% of the total MS patients in Cyprus. **Results**: The estimated prevalence of Cyprus was 198:100,000, with the district of Famagusta associated with the highest prevalence (57:100,000). The male to female ratio was1.6:1 and the mean age during exacerbation of the disease was 37.4 for females and 38.7 for males. The distribution of incidents according to place of birth was not statistically significant ($p = 0.152$); but the distribution of incidents by place of residence at the time of diagnosis was statistically significant ($p = 0.049$). Family history had no any statistical significance ($p=0.246$). The majority of the patients (66.2%, $p=0.038$) reported to be married during the disease diagnosis and 22.5% were serious smokers ($p=0.81$).Moreover, 0.74% out of the primary progressive and 0.49% out of the secondary progressive patients died as a result of the disease. **Conclusions:** The prevalence was higher than the expected, higher than the official reported by the Atlas of MS 2013 and disproportional to the global median prevalence of 90/100,000.Parameters like profession and smoking habit had no significance versus the disease of MS.

Keywords: *multiple sclerosis, MS incidence, MS prevalence, relapsing-remitting, multifactorial, autoimmune, neurodegenerative*

Cite This Article: Elena Charalambidou, Marios Pantzaris, and Ioannis Patrikios, "Multiple Sclerosis in Cyprus: A Fourteen Year (2000-2014) Epidemiological Study." *American Journal of Epidemiology and Infectious Disease*, vol. 4, no. 1 (2016): 1-9. doi: 10.12691/ajeid-4-1-1.

1. Introduction

MS is a chronic disease of the central nervous system (CNS) where the destruction of the myelin sheath surrounding neurons, results in the formation of plaques. It is a neurodegenerative, demyelinating diseaseand is characterized as **multifactorial** and **autoimmune** [1].

MS results from the interplay between environmental factors and a susceptible genetic background. These factors trigger a cascade of events involving the engagement of the immune system, inflammation of myelin, axons and glia, factional recovery and structural repair, gliosis and neurodegeneration [2].

Recent research has shown that multiple variables dynamically interact and many complex interrelated processes are simultaneously involved for the disease pathogenesis. Diseases, such as systematic lupus erythematosus, myasthenia gravis, ankylosing spondylitis, uveitis and inflammatory bowel disease have been reported to be associated with MS [3].

The World Health Organization and Multiple Sclerosis International Federation have estimated that about 60% of patients with MS will no longer have full ambulatory function twenty years following diagnosis of the disease [4].

All present, available disease modifying therapies do not cure MS but they do have some degree of efficacy on slowing the disease evolution by reducing the severity and frequency of relapses and/or slowing the disability progression; moreover, they increase longevity. [5] On the other hand all therapies are associated with several site effects affecting patients' quality of life.

Diagnosis of MS requires a neurological examination, patient history, and a series of tests including MRI, spinal fluid analysis, blood tests, and evoked potentials. [6] Diagnostic criteria require evidence of dissemination of neurologic signs and symptoms in space and time, based on anamnestic, clinical and paraclinical evidences. The most recently developed diagnostic criteria are the McDonald criteria. [7] Patients are evaluated based on the Expanded Disability Status Scale (EDSS), a rating that ranges from 0 to 10, with higher scores indicating more

severe disability, on MRI showing lesions and on documented clinical relapses.

According to the 2013 Atlas of MS, the estimated number of people living with the disease worldwide has increased by9.5% from 2.1 million in 2008 to 2.3 in 2013. The global median prevalence increased from 30 in 2008 to 33 per 100,000 in 2013.[8] The prevalence in Eastern Europe, where Cyprus is located, is reported to be 170 per 100,000.

The symptoms of the disease can start anywhere between 10 and 88 years of age, but the onset is usually between 20 and 40 years, with a **mean of 32 years**. [8] As with all immune-mediated diseases, MS behaves likewise with females being affected more frequently than males, **1.4-3.1** times as many women than men. [9] Moreover, there is a specific **geographic** distribution of MS around the world. A significantly higher incidence of the disease is found in the northernmost latitudes of the northern and the southern hemispheres compared to southernmost latitudes. Furthermore migration studies show that if the exposure to a higher risk environment occurs before the 15th year of age the migrant behaves like a local person assuming the higher risk of the environment [10].

Generally speaking, the prevalence of MS varies by location and generally increases the further one travels from the equator in either hemisphere. Prevalence is higher in North America and Europe (140 and 108 per 100,000 respectively) and lowest in Sub-Saharan Africa and East Asia, at 2.1 and 2.2 per 100,000 respectively (Figure 1). [8] It remains unclear whether this altered incidence represents an environmental influence, genetic difference, or variable surveillance [11].

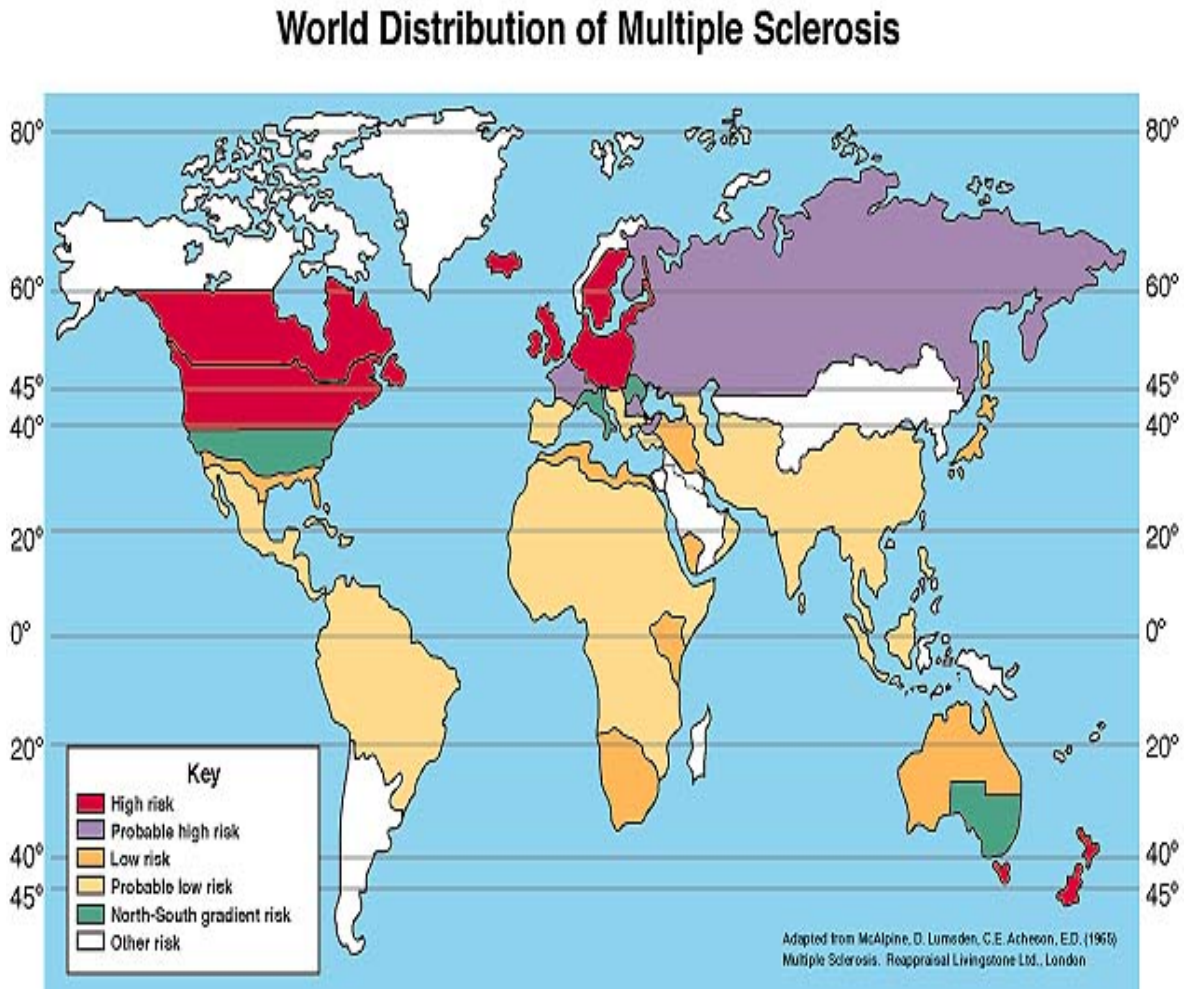

Figure 1. World Distribution of Multiple Sclerosis [10]

Lately, epidemics of MS provided further evidence of the importance of the **environmental** factors in relation to MS. The most notable one was described on the Faroe Islands after they were occupied by British troops in World War II [10].

Several population studies show differences in MS incidences between different populations. Lapps in Scandinavia have shown to be resistant to the disease contrary to the expectations based on their geographic distribution. Native Americans and Hutterites who frequently suffer from MS as opposed to other residents of the North American population is another good example. It has not been yet explained why these obvious inconsistencies of the disease's distribution are observed. [10].

It has also been reported that the incidence of MS in first degree relatives is twenty (20) times higher than in general population, suggesting involvement of **genetic** factors. We know that MS is more common in family members of people with MS. Some authorities say it is up to eighty (80) times more common in first degree relatives like brothers and sisters or children of a person with MS. [12] Monozygotic tween studies show a rate of 30% and dizygotic a rate of less than 5% suggesting that both genetic factors and environmental exposure are important to the disease pathogenesis [12].

A follow up study of the actual genes involved in determining susceptibility to MS showed, as expected, that MS is not inherited as a result of a single gene, as in diseases like cystic fibrosis or muscular dystrophy. The susceptibility to MS is the result of the interaction of several genes. As a result, predicting occurrence of MS in offspring is not possible at present [12].

Some published studies report an association between MS and age at Infection with common viruses such as mumps after 15 years of age (odds ratio = 2.3, 95% CI = 1.2–4.3) or measles after age 15 years of age (odds ratio = 2.8, 95% CI= 0.8–9.1). Individuals who suffered from infectious mononucleosis, a marker of late infection with the Epstein-Barr virus, have an increased risk of multiple sclerosis [13].

In recent years, prospective cohort studies revealed that deficiency of vitamin D and tobacco smoking are important for the pathogenesis in amultifactorial way. [14] The association between smoking and multiplesclerosis is positive but of modest effect. Numerous mechanisms have been proposed to explain the adverse effects of smoking on multiple sclerosis – including effects on the immune system and immunomodulatory effects, demyelination, and disruption of the blood–brain barrier (BBB)- but all remain speculative [15].

There are a number of major stages that occur in the disease, including activation and remission. At each of these major stages, specific genes are activated. Those genes express proteins and it is believed that these proteins could have the ability of switching the disease on and off [16].

Four disease courses have been identified in multiple sclerosis (Figure 2):

Benign MS: is the mild condition of the disease where the patient experiences relapses without disability progression.

Relapsing-remitting MS (RRMS): is the most common disease course characterized by clearly defined attacks of worsening neurologic function. These attacks are also called relapses, flare-ups or exacerbations and are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease. [17] If untreated, about 50 percent of people with RRMS become **secondary-progressive (SP)** within a decade of the initial diagnosis [6].

Secondary-progressive MS (SPMS): It follows after the relapsing-remitting course, usually within 10 to 15 years. Most people who are initially diagnosed with RRMS will eventually switch to SPMS, which means that the disease will begin to progress more steadily (although not necessarily more quickly), with or without relapses [18].

Primary-progressive MS (**PPMS**): is characterized by steadily worsening neurologic function from the beginning. Although the rate of progression may vary over time with occasional plateaus and temporary, minor improvements, there are no distinct relapses or remissions. About 10 percent of people with MS are diagnosed with PPMS [19].

Progressive-relapsing MS (PRMS) is the rarest form of MS, representing about 5 percent of MS patients. People with PRMS have clear relapses combined with a steady progression of the disease. [17]

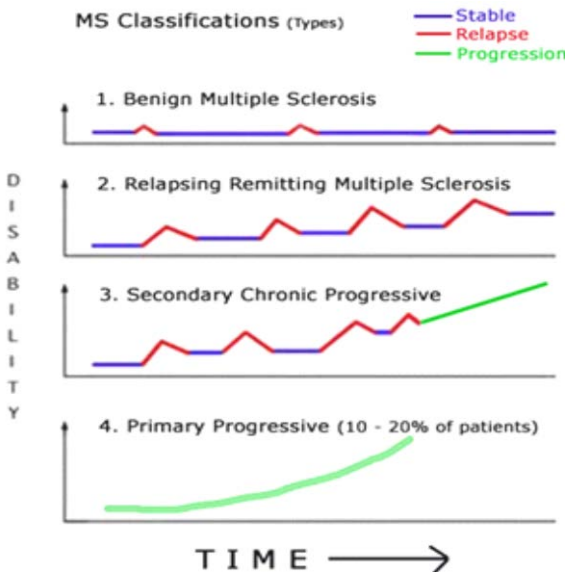

Figure 2. MS classifications (types) [20]

The development of disease progression (SPMS, PRMS, PPMS) is responsible for permanent long-term disability and it supervenes in about80% of RRMS participants after 20 to 25 years. After 15 to 18years, about 50% of participants need assistance to walk, are confined to a wheelchair, bed, or die. [21] PPMS is characterized, from the beginning, by a slow worsening of neurological deficits without experiencing attacks, and PRMS by a progressive course from onset with attacks and continuing progression. Natural history studies provide little support for the concept that progression is related primarily to a succession of attacks, indicating that attacks do not play a major role in long term disability. Preventing progressive disability is the key therapeutic goal for MS. [21].

Early MS symptoms include weakness, tingling, muscle stiffness, thinking problems, and urinary problems. [22] Other signs are fatigue, numbness, visual disturbances, bladder problems, mobility issues, and more [5].

This scientific work will present a totally novel study since there are no previous similar or comparative studies in reference to Cyprus. Until today, Cyprus has no data records out of scientific studies to support any specific crucial epidemiological information so to contribute to the international movement of controlling the disease. Now we are reporting a well-documented epidemiology study results, out of a properly designed research for Cyprus.

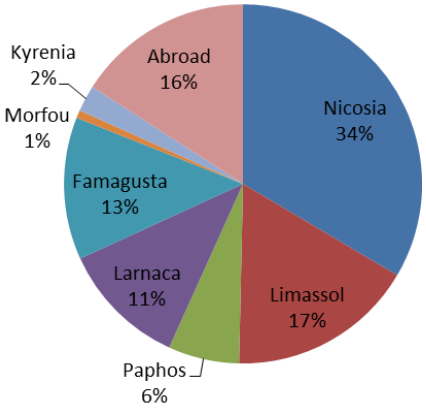

Figure 3. The distribution of patients according to the province of birth

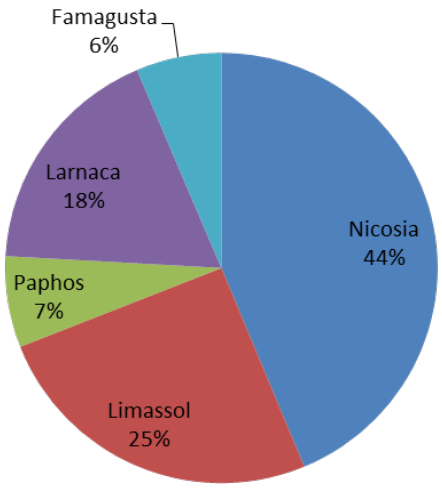

Figure 4. The distribution of patients according to the province of residence

2. Methodology

The present study is a descriptive as well as a comparative study. The research accessed information from the CING, a bi-communal, non-profit, research, medical and academic center established in 1990. The 80% out of the Cyprus MS population is under the medical observation of the CING. Thus, it is the only place on the island, able to have a complete record of the national MS patients' archives. Dealing with patients' files and personal data, a confidentiality agreement in compliance with the Processing of Personal Data (Protection of Individuals) Law 138 (I) 2001, and all its amendments was signed.

Out of the total MS patients' files, we collected and evaluated 427patients. The eligibility criteria were to be diagnosed with MS, during the years 2000-2014, irrespective of the type of MS, Greek-Cypriots born in Cyprus or abroad but reside in Cyprus and diagnosed with MS according to the McDonald criteria. The information recorded concerned both sexes, all ages and on any treatment. Birth date, age at diagnosis, classification of disease, place/location of the patient at the time of disease onset, current residence area, occupation, date of first symptom, family history related to MS, smoking habit were also recorded.

The prevalence was calculated according to the Cyprus population of 2013 (858,000, according to the Statistical services of the Ministry of Internal Affairs Cyprus). The statistical analyses included descriptive statistics (frequencies/percentages for categorical variables and mean/standard deviation for continuous variables). The chi-squared test was used to assess associations between categorical variables while the t-test and the analysis of variance were used to examine whether the mean values of continuous variables were different across the groups of categorical variables. If necessary, non-parametric tests were used. Unless stated differently, a p-value of less than 0.05 was considered as statistically significant.

3. Results

We studied 427 MS patients admitted at the Cyprus Institute of Neurology and Genetics during the fourteen year period between the years 2000-2014, out of total 1700 MS patients, with an average annual rate of 28.5 ± 15.5 MS patients. The Cyprus population in 2013 was 858,000 with a total of 1700 MS patients, a prevalence of 198:100,000. Table 1 shows the MS prevalence by province. The district of Famagusta had the highest prevalence of 207 per 100,000.

Table 1. Prevalence of MS in Cyprus (per 100,000 population) by district in 2013 [23]

Residence	Prevalence/ 100,000
Nicosia	202
Limassol	150
Larnaca	187
Pafos	108
Famagusta	207
Total	198

We examined the frequency of MS according to the place of birth (p=0.568) and place of current residence (p=0.365). All of the provinces show increase of frequency when estimated by province of current residence, except the district of Famagusta, where a decrease is noted. The districts of Morfou and Kyrenia do not appear at our frequency estimation by current residence, because after 1974, these are totally occupied areas.

Out of 427 patients, 260 were female (60.89%) and 167 male (39.11%), demonstrating a female to male ratio of 1.6:1(p=0.58). The frequency of MS in females, with the exception of 2006, 2010 and 2013, had always exceeded that of the male patients (Figure 5).

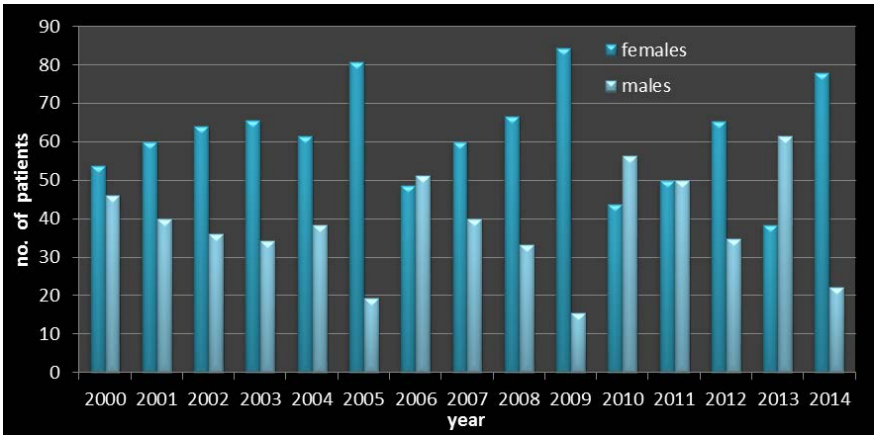

Figure 5. MS frequency by gender (2000-2014)

The time of diagnosis was noted according to region of birth and region of current residence. Through the years, most patients were born in Nicosia but in 2005 and 2007 most of them were born in Famagusta and Limassol respectively (Table 2). The distribution of incidents according to place of birth was statistically non-significant (p = 0.152). On the other hand, the distribution of incidents by place of residence at the time of diagnosiswas statistically significant (p = 0.049). While most of the incidents have been found to be within the district of Nicosia this was changed for the years 2004 and 2006 with the district of Limassol becoming the one with the highest number of incidents (Table 3).

Table 2. Number of MS patients/ Year diagnosis /Place of Birth

City	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Nicosia	18	8	11	16	5	5	7	9	11	12	5	6	10	7	11
Limassol	5	4	1	4	6	5	6	12	3	7	4	4	6	2	2
Paphos	3	2	2	0	3	0	2	3	5	4	1	2	1	0	0
Larnaca	5	1	1	5	7	0	5	5	2	7	1	2	3	2	1
Famagusta	5	6	6	0	4	10	7	2	2	4	1	1	1	1	1
Morfou	0	1	0	3	0	1	1	0	0	0	0	0	0	0	0
Kyrenia	1	1	1	0	0	1	1	2	1	1	0	1	0	0	0
Abroad	3	3	5	3	2	5	12	6	4	9	5	2	2	2	4
Total	40	26	27	31	27	27	41	39	28	44	17	18	23	14	19

Table 3. Number of MS patients/ Year of diagnosis / Current Residence

City	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Nicosia	19	12	11	17	8	10	12	19	13	19	7	6	10	7	15
Limassol	8	5	3	3	11	10	15	14	7	9	5	6	4	3	4
Paphos	1	3	1	0	2	2	1	2	5	3	1	4	3	1	0
Larnaca	7	2	10	8	6	5	11	2	2	9	4	2	5	1	1
Famagusta	5	4	2	1	0	1	3	2	1	4	0	1	1	2	0
Total	40	26	27	30	27	28	42	39	28	44	17	19	23	14	20

Mean age at diagnosis was 37.4 ± 11 years (95% CI 35.96,) for females and 38.7 ± 12 years (95% CI 36.80) for males, presenting a non-significant difference between men and women (p= 0.127).The most frequent range of age at diagnosis was distributed equally between the ages of 25 to 34 and 35 to 44 (28.46% and 28.72% respectively) (Table 4). On the other hand, patients mostly got the first symptom between the age range of 25 to 34(35.64%).

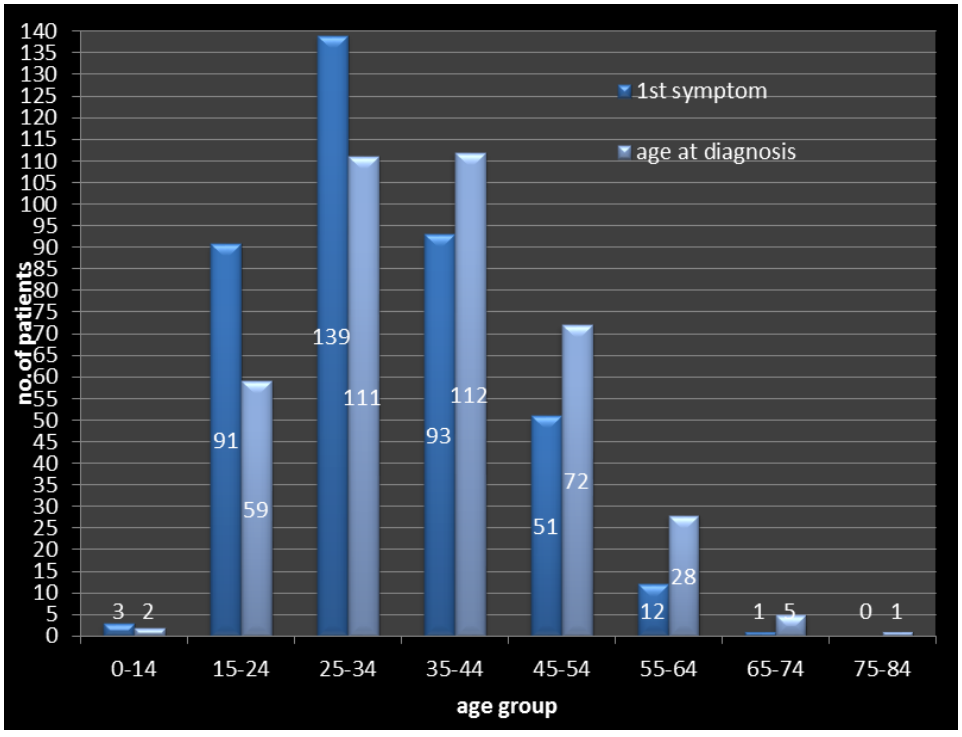

Figure 6. Number of MS patients by age at first symptom and by age at diagnosis

Table 4. Age at first symptom, at diagnosis and in 2014

Age range	1st symptom	Age at diagnosis	Age today (2014)
0-14	3	2	0
Population (%)	0,77	0,51	
15-24	91	59	11
Population (%)	23,33	15,13	2,82
25-34	139	111	83
Population (%)	35,64	28,46	21,28
35-44	93	112	112
Population (%)	23,84	28,72	28,72
45-54	51	72	97
Population (%)	13,08	18,46	24,87
55-64	12	28	58
Population (%)	3,08	7,18	14,61
65-74	1	5	29
Population (%)	0,26	1,28	7,44
75-84		1	1
Population (%)		0,26	0,26

The number of patients who got their first symptom was bigger than the number of patients who got their first diagnosis for the age range of 25 to 34. For ages above 34, the people who got diagnosed were more than those who got their first symptom (Figure 6).

The majority of the patients (46.6%) were diagnosed within months to one year from the first symptom. But 6.8% of the patients took up to 8 years to be diagnosed. A small percentage took more than 9 years from first symptom to diagnosis (Figure 7).

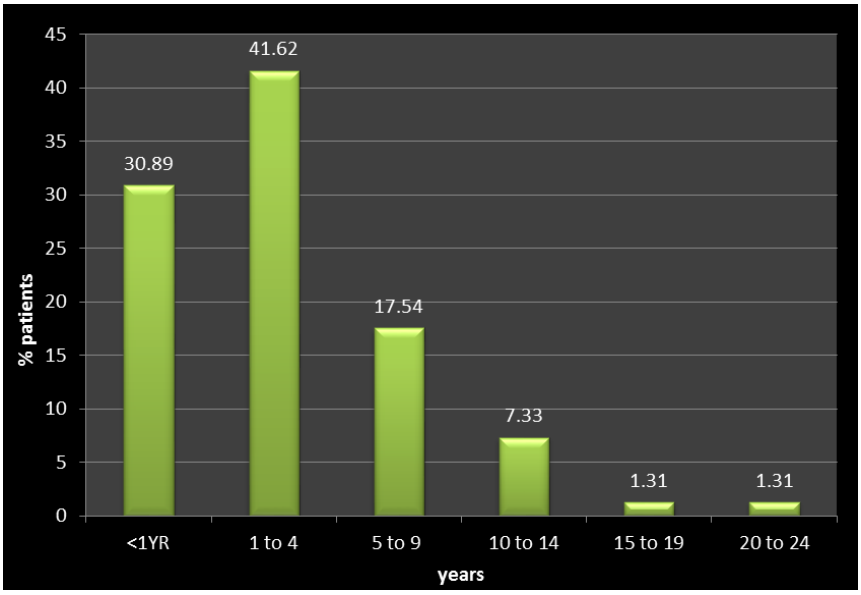

Figure 7. MS Patients (%) by time (in years) from 1st symptom to diagnosis

Out of 427 MS patients, 326 (76%) had no family history for the MS disease. There was no statistically significant deference even after MS sub-type analysis Vs family history (p=0.246).

The diagnosed onset married patients was statistically significant Vs single patients (p=0.038). The 74.7% of the studied samples were non-smokers without statistically significant difference (p=0.81) Vs smokers (Table 5).

Table 5. Marital status, occupation and smoking habit

Marital status (n (%))	
Single:	117 (27.4)
Married:	283 (66.2)
Ex-Married:	24 (5.6)
NA:	3 (0.8)
Occupation (n(%))	
Professionals:	258 (60.4)
Students:	38 (8.9)
Housewives:	50 (11.7)
None:	64 (15)
Retired:	17 (4)
Total:	427
Smoker/non-smoker (n(%))	
Yes:	96 (22.5)
No:	319 (74.7)
Ex:	7 (1.6)
NA:	5 (1.2)

Table 6. Type of MS vs gender

Type of MS	Male	Female	Total
RR	113	208	321
Population (%)	67.66	80	75.18
PP	20	20	40
Population (%)	11.98	7.69	9.37
SP	25	18	43
Population (%)	14.97	6.92	10.07
CIS	7	12	19
Population (%)	4.19	4.62	4.45
Total	165	258	423
Population (%)	100	100	100

As expected, the results depending on the most frequent type of MS was statistically significant (p=0.014). The most frequent type of disease among the 423 MS patients was the Relapsing-Remitting (RR) with 321 patients, followed by 43 with Secondary Progressive (SP), 40 with

Primary Progressive (PP), and lastly 19 patients with Clinically Isolated Syndrome (CIS) (Table 6).

Investigating the types of MS according to the year of diagnosis (Figure 8), the RR type predominated (p=0.056). Out of the 40 patients diagnosed in 2000, 26 were RR type and remained the same till 2014, 14 years later (65%). For the patients diagnosed in2004, 18 out of 27 were RR type and remained the same till 2014.

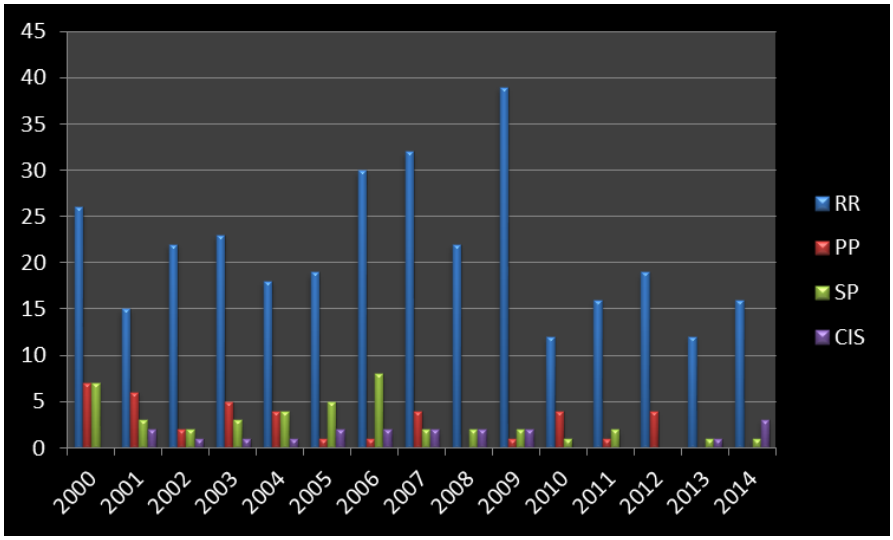

Figure 8. Number of MS patients by the Year of diagnosis and by the type of MS today

Both males and females were mostly diagnosed with the RR type (68.48% and 80.62% respectively) with p=0.014. Even though RR was more common among women, the CIS type appeared at same rates in men and women. Although it was clear that MS affected more women than men, the trend changed when evaluated the PP and SPtypes of the disease. For the PP type equal numbers of male and female patients were diagnosed and the number of men with SP type exceeded that of women. (Table 6).

4. Discussion

This is an epidemiological study for MS for the European Island of Cyprus. We gathered information out of a homogenous sample, a total of 427 MS patients representing the 25% of the total MS patients within the island. All patients were Greek Cypriots, born in Cyprus or abroad, residing in Cyprus and diagnosed between the years 2000 and 2014. Out of the 427 patients, 3 males and 2 females (1.2%) were dead as a result of the disease before the launch of our study (p=0.336).

In Cyprus, currently there are about 1700 MS registered patients. The prevalence has been showed to be 198 per 100,000, shockingly higher than the prevalence estimated in 1991(44.5/100,000), higher than the official estimate of Atlas of MS 2013(178/100,000) and definitely disproportional to the global median prevalence of 90/100,000. [24] This finding is in accordance with the fact that the prevalence of MS is increasing but is strikingly higher than the previously reported regional prevalence of 52-83/100,000. [24] One cannot attribute this rise to a specific cause, as it could reflect to a better case ascertainment, earlier diagnosis or demographic factors or all of these factors combined.

Today the prevalence by province shows the region of Famagusta to be the highest. The frequency of MS according to place of birth (p=0.568) and according to current residence (p=0.365) shows increase in all provinces except the district of Famagusta. The fact that the number of patients decreases in this area, when investigating current residence and increases in the rest of the districts is attributed to the fact that after 1974, half of the Famagusta area was occupied; and the locals were distributed to the rest of the island's districts.

In accordance with previous studies our findings correlate, as far as the incidences among male and female population concerns, with females being affected more frequently than males. The same pattern was noted when we examined the ratio according to the different types of MS. The results based on the distribution of MS by gender have been showed to be statistically significant (p=0.014).

The mean age at diagnosis was estimated to be 37.4 ± 11 years for females and 38.7 ± 12 years for males, without any statistically significant difference between them (p=0.127).MS symptoms had been showed to begin anywhere between 14 and 84 years of age, but onset was usually between 25 and 54 years, with a mean of 39.37 years. The 29% of the patients ranged between the ages of 25 to 34 and 35 to 44, but 35.64% were between 24 to 34 years old at the first symptom; an indication that MS mostly attacks during adulthood. Most of the patients (35.64%) had their first symptom between the age of 24 to 35 years and diagnosed during the age ranges of 25 to 34(28.5%) and 35 to 44(28.7%). By the age of 34 years, 60% of the population(233 out of 390) under investigation got their 1st symptom and 73% (284 out of 390) diagnosed by the age of 44. In general, most of the patients, 185 out of 397 (46.6%), were diagnosed within months to a year after experiencing their first symptom. Some extreme cases have been diagnosed after 10 years from the time of the first symptom. This is probably due to the characteristics of the disease that is unpredictable with unique evolution for each individual. This could also be due to the relapse history of those patients, exhibiting long lasting remissions; the contagion phenomenon that is well defined by previous researchers [25].

Multiple sclerosis (MS) is known to accumulate within families with history on the disease. Our data show that

76% out of the total studied population (326 out of 400) have no family history. Previous published data indicated that MS inheritance is only about 2 to 4%; and family members who have MS tended to develop the disease at around the same age. However, family history does not predict whether one family member will ever develop the disease and to what extent. The magnitude of the familial risk remains uncertain.

Moreover, out of our study, we concluded that 2 out 3 MS patients were married and 22.5% were regular smokers without any statistical significance, suggesting no any correlation between smoking and the disease onset and/or frequency. Amongst them, the highest percentage, 76.6%, had the RR type of MS (321 patients out of 423). This finding coincides with all previous studies stating that patients with MS display variable clinical course. At onset, approximately 10% of patients display a primary progressive form (PP), whereas the remainder start out with a relapsing remitting form (RR);with most of them switching to a secondary progressive form (SP) within 10to 30 years.[26]This can be due to the medications that reduce the number and severity of the relapses and slow down the progression of the disease.

Our study confirms the already existing knowledge that the majority of the MS population is first experiencing RR type, followed by SP(68.48% and 80.62% respectively), with much less PP incidences. Our data have also indicated that the population diagnosed with Clinically Isolated Syndrome (CIS) appears at same rates in men and women. Although it is clear that MS affects more women than men, the trend changes when it comes to the PP and SP types of the disease. We see equal numbers of male-female patients with PP type and the number of men with SP type exceeds that of women.

Available disease modifying therapies delay disease progression, disability and increase longevity. [5] Out of 427 patients, 313 are still working and 50 are housewives.

Not all of our findings have statistically significant outcomes but they have clarified important issues leading to meaningful conclusions. Moreover, these new epidemiological findings on MS prevalence can lead to some re-assessments of previously held concepts about the disease within the Island of Cyprus. Treatment and stages of MS are important issues to be discussed, but this is beyond the scope of this study.

Concluding, we can report that Cyprus, the smallest country of European Union (EU), besides Malta, has very high prevalence of MS incidences among the rest of the EU countries. It is higher than Sweden with 189 incidences (indicated as the country with the highest number of incidences within EU) and Hungary with 176 incidences per 100,000 (second in the Atlas of MS) until now. Canada is the country that reports the highest prevalence of 291 incidences per 100,000 populations. There is no any reasonable logic to support the “whys” of these findings but epidemiological studies can always be the vehicle for possible answers.

Abbreviations

MS: Multiple Sclerosis, CING: Cyprus Institute of Neurology and Genetics, RR: relapsing-remitting-, SP: secondary progressive, PR: primary progressive, PR: progressing relapsing.

Authors’ Contribution

EC participated in the study design, data abstraction, data processing, statistical analyses and drafting of the manuscript. MP coordinated and participated in the data abstraction and study design. IP suggested the theme of this investigation, coordinated its progress and study design, reviewed and verified all abstracted data and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Thanks to Ms. Niki Nicolaou Papaioannou, CING employee who gathered all the patients’ files and Lenia Papadopoulou who supplied me with some statistical information. We also thank Dr George Nikolopoulos for his guidance on the data and statistical analyses.

References

[1] Centers for Disease Control and Prevention. http://www.cdc.gov/vaccinesafety/Vaccines/multiplesclerosis_and_hep_b.html

[2] Pantzaris C.M, Loukaides G.N, Ntzani E.E, Patrikios S.I; A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomized, double-blind, placebo-controlled proof-of-concept clinical trial BMJ Open 2013.

[3] Sadovnick A.D,Dyment D,Ebers G.C; Genetic Epidemiology of multiple Sclerosis; Epidemiologic reviews, 1997, vol.19, No. 1: 99-106.

[4] Aljumah M, Alroughani R, Alsharoqi I, et.al; Future of Management of Multiple Sclerosis in the Middle East: A Consensus View from Specialists in Ten Countries; Multiple Sclerosis International, 2013, Article ID 952321.

[5] Multiple sclerosis association of America; http://www.mymsaa.org/about-ms/overview/

[6] Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vecsei L and Milanov I; The epidemiology of multiple sclerosis in Europe; European Journal of Neurology 2006,13:700-72.

[7] Koutsouraki E, Fotakidou A, Kalatha T, Baloyannis S. Epidemiologic Data of Multiple Sclerosis in Northern Greece during the Last Thirty Years (1979-2008). American Journal of Epidemiology and Infectious Disease, 2013, Vol. 1, No. 1, 1-7.

[8] Atlas of MS2013; multiple sclerosis international federation *2013.*

[9] Harbo H.F, Gold R, Tintore M; Sex and gender issues in Multiple Sclerosis.2013; 6(4):237-248.

[10] http://library.med.utah.edu/kw/ms/epidemiology.html.

[11] Cleveland clinic, center of continuing education. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multipesclerosis/.

[12] Hansen T, Skytthe A, Stenager E, et al.; Concordance for multiple sclerosis in Danish twins: an update of a nationwide study; MultScler 2005; 11:504-510.

[13] Hernán M.A; Zhang S M; Lipworth L; Olek M J; Ascherio A; Multiple Sclerosis and Age at Infection with Common Viruses; May 2001, Volume 12;3:301-306.

[14] Klaus Lauer; Notes on the Epidemiology of Multiple Sclerosis, with Special Reference to Dietary Habits; Int J MolSci; 2014 Mar; 15(3): 3533-3545.

[15] Belbasis L, Bellou V, Evangelou E, Ioannidis J, Tzoulaki I; Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses; Lancet Neurol; 2015 Mar;14(3):263-73.

[16] National search for proteins that cause MS; THE UNIVERSITY of ADELAIDE; Wednesday, 26 August 2009; http://www.adelaide.edu.au/news/news35163.html.

[17] National Multiple sclerosis society; http://www.nationalmssociety.org/What-is-MS/Types-of-MS.

[18] Multiple Sclerosis; Patient;http://patient.info/health/multiple-sclerosis-leaflet.

[19] Brichford C; Understanding the Different Types of Multiple sclerosis; everyday HEALTH; http://www.everydayhealth.com/multiple-sclerosis/symptoms/multiple-sclerosis-types.

[20] Out of the unpublished library records of the Cyprus Institute of Neurology and Genetics (CING)

[21] Filippini G, Del Giovane C, Vacchi L, D'Amico R, Di Pietrantonj C, Beecher D, Salanti G; Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis (Review); Cochrane reviews; The Cochrane Library; 2013; 6.

[22] WebMD; http://www.webmd.com/multiple-sclerosis/default.htm.

[23] Unpublished data, personal communication, Dr Marios Pantzaris, CING.

[24] Atlas of MS/ MS International Federation; http://www.msif.org/about-us/advocacy/atlas/.

[25] Wang YC, Meyerson L, Tang YQ, et al. Statistical methods for the analysis of relapse data in MS clinical trials. J NeurolSci; 2009; 285: 206-11.

[26] Deshpande R, Kremenchutzky M, Rice G; The natural history of multiple sclerosis; Neurologic Clinics;1995;13:119-146.