INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) that is characterized pathologically by inflammation, demyelination, and, ultimately, axonal loss ***(Frohman et al., 2006; Compston and Coles, 2008).***

Diagnosis of MS is based on the concept of the disease's dissemination in both space and time. Although MS can be diagnosed on clinical grounds alone, magnetic resonance imaging (MRI) can be used to support or establish the diagnosis, as well as to track disease progression.

In general, the researchers found that MS prevalence has increased dramatically in that 5 year span, up 10% and now affecting 2.3 million people worldwide. Whether this is due to a true intrinsic increase in prevalence or whether the condition is being better diagnosed and reported is not clear. For instance, the number of neurologists worldwide have increased by 30%, which might mean that MS is being better diagnosed and reported. Either way, we now know the prevalence is much higher than we previously thought ***(Multiple Sclerosis International Federation, 2013).***

There are four clinical phenotypes of MS. Initially, more than 80% of individuals with MS experience a relapsing remitting disease course (RRMS) characterized by acute attacks

of neurological symptoms and signs followed by complete or incomplete remission. Progressive disease that follows an initial period (often many years) of RRMS, much of patients will develop a secondary progressive course of disease (SPMS). Another 10% to 20% of patients with MS are diagnosed with primary progressive MS (PPMS) it is a progressive disease from the onset without any attacks or remission ***(Selchen et al., 2012).***

Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system (CNS), which is thought to be caused by a complex interplay between genetic and environmental risk factors ***(Birth Patterns of Neurological Disorders, 2009).***

It is not clear why MS develops in some people and not others. A combination of genetic and environmental factors appears to be responsible ***(Daroff et al., 2014).***

These factors may increase the risk of developing multiple sclerosis including Age: MS can occur at any age, but most commonly affects people between the ages of 15 and 60,Sex: Women are about twice as likely as men are to develop MS, Family history: If one of your parents or siblings has had MS, you are at higher risk of developing the disease, Certain infections: A variety of viruses have been linked to MS, including Epstein-Barr, the virus that causes infectious mononucleosis, Race: White people, particularly those of

Northern European descent, are at highest risk of developing MS. People of Asian, African or Native American descent have the lowest risk, Climate: MS is far more common in countries with temperate climates, including Canada, the northern United States, New Zealand, southeastern Australia and Europe, Certain autoimmune diseases: You have a slightly higher risk of developing MS if you have thyroid disease, type 1 diabetes or inflammatory bowel disease, Smoking: Smokers who experience an initial event of symptoms that may signal MS are more likely than nonsmokers to develop a second event that confirms relapsing-remitting MS and Vitamin D Deficiency ***(Wingerchuk, 2014).***

Vitamin D is a principal regulator of calcium homeostasis. However, recent evidence has indicated that vitamin D can have numerous other physiological functions including inhibition of proliferation of a number of malignant cells including breast and prostate cancer cells and protection against certain immune mediated disorders including multiple sclerosis (MS). The geographic incidence of MS indicates an increase in MS with a decrease in sunlight exposure. Since vitamin D is produced in the skin by solar or UV irradiation and high serum levels of 25-hydroxyvitamin D (25(OH)D) have been reported to correlate with a reduced risk of MS, a protective role of vitamin D is suggested. Mechanisms whereby the active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) may act to mediate this protective effect are

reviewed. Due to its immunosuppressive actions, it has been suggested that $1,25(OH)_2D_3$ may prevent the induction of MS ***(Hayes et al., 2011).***

A number of studies have indicated that the risk of MS is strongly associated with place of residence in early life ***(Saastamoinen et al., 2012).*** Further, early life and gestational events have frequently been suggested to contribute to MS susceptibility ***(Fernandes et al., 2009).***

Findings of seasonal birth patterns that differ significantly from the general population suggest that environmental factors acting in early life or in the intrauterine period are important for disease susceptibility ***(James, 1995).***

Risk factors for development of multiple sclerosis (MS) are still a matter of debate. Vitamin D deficiency and season of birth are among the most investigated environmental factors associated with the disease ***(Wiberg and Templer, 1994; Willer et al., 2005).***

Several international studies suggest that birth in spring is a substantial risk factor for MS ***(Bayes et al., 2010).*** Season of birth as a potential risk for MS in different geographical regions of Egypt is to be investigated.

AIM OF THE WORK

The aim of the study is to test the hypothesis whether multiple sclerosis is associated with a certain season of birth in Egyptian patients or not and its relation to vitamin D deficiency.

DEFINITION OF MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a chronic neurological disorder affecting central nervous system. It is classified as the most common neurological cause of disability in young adults. However the aetiology is not well understood, but most propably multifactorial involvement is the most convenient theory till now ***(Mckay et al., 2016)***. It is characterized by inflammation, demyelinaion, axonal loss and degeneration. There is a debatae about neurodegenerative character of the disease, whether inflammation initiates neurodegeneration or neurodegeneration occurs independent of inflammation ***(Losy, 2013).***

Multiple sclerosis (MS) is one of the world's most common neurologic disorders, and in many countries it is the leading cause of nontraumatic neurologic disability in young adults ***(Tullman, 2013).***

It frequently leads to working inability, especially in the patients with a severe disease course to a reduced quality of life both in patients and caregivers, and to excess mortality ***(National Multiple Sclerosis Society, 2017).***

Several clinical courses are described in MS ***(Leray et al., 2010);*** 85% of patients are diagnosed with RRMS. 75% of RRMS patients will develop secondary progressive MS (SPMS) within 10-15 years of the initial diagnosis. 10-15% of MS patients, develop progressive disability from the start, so-

called primary progressive MS (PPMS) ***(Lublin et al., 2014).*** An international panel in 2013 added clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS) as MS phenotypes ***(Lublin et al., 2014).***

Clinically isolated syndrome (CIS) is "the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill criteria of dissemination in time***(Lublin et al., 2014***).

However, Multiple sclerosis can be diagnosed at the time of the first attack when Dissemination in both space and time demonstrated on a single MRI scan with evidence of both chronic and acute enhancing lesions ***(Kreiger, 2016).*** RIS is a syndrome where incidental imaging findings suggest inflammatorsy demyelination without clinical signs or symptoms. An RIS patient should be followed prospectively for other positive findings enhancing diagnosis of MS as cerebrospinal fluid (CSF) findings, enhancing or spinal cord lesions ***(Lebrun, 2009).***

RRMS disease course marked by acute exacerbations (relapses) from which they typically completely or incompletely recover, with periods of relative clinical stability in between ***(Katz sand, 2015).*** A relapse is a patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection ***(Ross et al., 2012).***

SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations and till now there are no clear criteria to determine the transition point when RRMS converts to SPMS. PPMS is diagnosed by a clinically progressive course in absence of clinical exacerbations/relapses ***(Lublin et al., 2014).***

PPMS is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions. PPMS can be further characterized at different points in time as either **active** (with an occasional relapse and/or evidence of new MRI activity) or **not active**, as well as **with progression** (evidence of disease worsening on an objective measure of change over time, with or without relapse or new MRI activity) or **without progression** ***(Miller, 2007)***.

Phenotype modifiers regarding the presence of recent disease activity and progression have been added to further clarify disease status including two disease modifiers, activity and progression ***(Katz sand, 2015).*** Activity is assessed by clinical activity (relapses) and brain MRI activity, presence of gadolinium-enhancing lesions and/or new or unequivocally enlarging T2 lesions, in patients with relapsing and progressive phenotypes. Progression is assessed by a clinical yearly assessment. This is based on patient-reported history and objective findings on clinical examination, as there is lack of biomarkers needed for progression assessment ***(Katz sand, 2015).***

NEDA (No evidence of disease Activity) -4 is a new concept related to absence of disease activity in the context of MS. It takes into account the following four parameters: relapses; disability progression; lesion load and brain atrophy ***(Matta et al., 2016).***

No Evidence of Progression (NEP): A novel composite endpoint that measures the proportion of patients with no confirmed progression of disability status (EDSS), walking speed (T25-FW) and upper extremity function (9-HPT) and may represent a new outcome for people with PPMS ***(Matta et al., 2016).***

Recently, NEPAD is an A novel composite endpoint that measures the combined absence of disease activity (relapses and MRI activity) and progression (disability). NEPAD is similar to NEDA, but uses a composite endpoint (no confirmed disability progression by EDSS, 20% progression on timed 25 foot walk, and 20% progression on 9 hole peg test) to measure disability. This may represent a more comprehensive measurement of overall disease activity and progression for people with PPMS ***(ECTRIMS, 2017).***

Progression Independent of Relapse Activity (PIRA), a new endpoint that is intended to separate relapse activity from underlying activity and measure disability.“Patients who have disease progression have disability that’s irreversible, and PIRA is a way to measure that, PIRA represents an effective

way to understand the impact of disease progression and disability on quality of life ***(ECTRIMS, 2017).***

Epidemiology of MS:

MS is found in every region of the world, the estimated number of people with MS has increased from 2.1 million in 2008 to 2.3 million in 2013 The number of MS patients in Egypt in year 2013 according to the MS Atlas published by WHO is around 20000 patients and this number is increasing daily. Prevalence also varies considerably within regions. For example, the highest prevalence in Europe is 189 per 100,000 in Sweden, and the lowest is 22 per 100,000 in Albania ***(Multiple Sclerosis International Federation "MSIF" Atlas of, 2013)*** **(figure 1).**

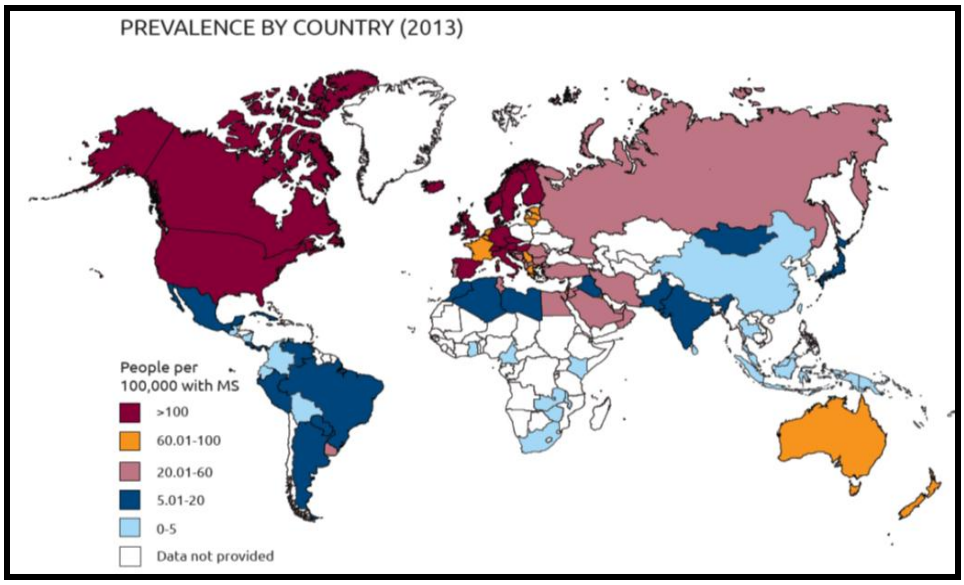

Figure (1): Prevalence of Multiple sclerosis by country ***(MSIF, 2013).***

Multiple sclerosis affects 2,5 million of people worldwide with a highly uneven geographical distribution, the large differences in the reported prevalence of MS indicate that there are regional risk factors for disease susceptibility Both genetic and environmental factors have been shown to be relevant in the pathogenesis of MS, while progress has been made in identifying etiological factors in multiple sclerosis, the cause of the disease is still not known ***(Goodin, 2014).***

It has been reported that the prevalence of MS varies according to latitude, for example, in South America, the prevalence for MS in Argentina considered a medium risk country for MS – is estimated to be 18 per 100,000, which is six times higher than the prevalence of 3.2 per 100,000 recorded for Ecuador, a low risk country for MS ***(Evans, 2013).***

There are large differences in the reported prevalence of MS, both within and between countries. Prevalence estimates from Norway are the highest in the world, with 203 per 100 000 inhabitants in a recent study ***(Berg-Hansen et al., 2014).***

In contrast prevalence rates in regions of Asia are below five per 100 000 inhabitants, a latitude gradient of prevalence has been identified, with a high prevalence in Northern Europe, North America, Australia and New Zealand, and a lower prevalence in South-America, Africa and Asia. There's a tendency towards higher prevalence and incidence in all investigated regions with time ***(Simpson et al., 2011).***

In a previous Egyptian retro-spective meta-analysis study in different referral centers, including five centers in Cairo metropolitan, and five other centers in different governorates, one center in each city of Alexandria in north Mediterranean coast, Mansoura, Tanta, and Zagazig in Delta, and Assiut in Upper Egypt, the prevalence of MS in Egypt was found to be 14.1/100,000 ***(Hashem et al., 2010).***

Another study is a part of door-to-door survey of major neurological disorders that was conducted in Al Quseir city, Red Sea Governorate, Egypt. The sample size was 33,285 persons, it found that a total of three cases of MS were diagnosed with an age-specific prevalence >17 years of 13.7/100,000 ***(El-Tallawy et al., 2016).***

About 2.3 million people have been diagnosed with this condition, the ratio of women to men with MS varies, and is considerably higher in some regions, such as East Asia where the female-to-male ratio is 3.0, and the Americas where it is 2.6. Middle Eastern and North African countries are in a low- to moderate-risk zone for MS based on the 2013 MS Atlas ***(Browne, 2014).***

Within region, there are countries where the ratio is considerably higher than average. For example, in Iran the ratio is 2.8 women to each man with MS, well above that for the Eastern Mediterranean region other studies indicate that the

ratio of women to men with MS has increased significantly over recent decades ***(Elhami, 2011).***

The reason for this difference in MS risk between men and women is not fully understood, and neither is the cause of the apparent increase in the ratio in many countries over recent decades, though it is likely to be caused by the interaction of changes in a range of social and environmental factors with underlying genetic differences. Published epidemiological research indicates that 2-5% of people with MS are diagnosed under the age of eighteen, there were an estimated 7,000 people under 18 with MS in the 34 countries, mainly in Europe, Eastern Mediterranean and North America and the pooled prevalence of pediatric MS in these 34 countries is 0.63 per 100,000 ***(Naci et al., 2014)***.

In a recent Egyptian study in Multiple Sclerosis Unit at Ain Shams University Hospitals (N=950) showed that MS is more common among females in Egypt, females represented 72% of subjects (female: male ratio=2.57:1) while the mean age of disease onset was 26.1±7.6 years ***(Zakaria et al., 2016).***

CLINICAL FEATURES OF MS

Multiple Sclerosis (MS) is not a diagnosis of exclusion and its diagnosis depends on certain features conclusive of specific syndromes according to areas affected with exclusion of other diagnoses by distinguishing red flags ***(Katz sand, 2016).*** One of the commonest clinical presentations of MS is acute onset of a partial transverse myelitis and the sensory symptoms are consistent with involvement of the dorsolateral cord. The course is usually days and begins to spontaneously recover over a few weeks ***(Cree, 2014)***. Brain MRI may be suggestive of MS accompanying transverse myelitis and will meet diagnostic criteria in the near future ***(Bourre et al., 2012).***

Various clinical presentations have been reported depending on the involved area of the CNS including physical, cognitive, and emotional disorders with different types of disease courses ***(Lublin, 2014)***. MS commonly affects young adults between the ages of 20 and 40 years, with a peak incidence at the age of 30 ***(Pena, 2013).*** Female to male ratio is 4:1 at adolescence, 2.5:1 in adulthood until age 45 to 49, and then 1:1.5 after the age of 50. This is indicative of a hormonal influence on MS risk or a gender defined genetic influence on immunologic activity ***(Cossburn et al., 2012)***.

Optic neuritis is also a common presentation in which acute unilateral decrease in visual acuity peaks within a few days and begins to recover within a few weeks ***(Optic Neuritis***

Study Group, 1991). Examination shows impairments in acuity, low contrast vision and color discrimination as well as an afferent papillary 0defect ***(Bermel and Balcer, 2013).*** Central scotomas are common and a variety of visual field defects are possible. Fundus examination is sometimes normal and optic disc swelling may be seen ***(Hickman et al., 2002).*** Red flags which are uncommon in MS include bilaterality and poor recovery, even without steroids ***(Bermel and Balcer, 2013).***

Brainstem or cerebellar syndrome is a common syndrome which has different clinical presentations such as diplopia which is the most common presentation, and can be bilateral due to internuclear ophthalmoplegia ***(Miller et al., 2012).*** Other presentations suggestive of MS include loss of sensation with eye movement abnormalities or in isolation. Vertigo resulting from vestibular pathways lesion and ataxia from a Cerebellar lesion ***(Miller et al., 2012).*** Red flags include isolated trigeminal neuralgia, third nerve palsy or complete ophthalmoplegia ***(Katz sand, 2016).***

Cognitive impairment is common in all phenotypes. It begins early and becomes more prominent in progressive than relapsing MS. It happens without clear simultaneous focal neurological manifestations ***(Katz sand, 2016).*** Paroxysmal symptoms are transient, recurrent and stereotyped such as vibrating or shock-like sensation with neck flexion (L'hermitte phenomenon), tonic spasms, trigeminal neuralgia, or paroxysmal dysarthria. And they must be recurrent over at least