INTRODUCTION

Multiple sclerosis (MS) is a complex immune mediated disorder of the Central Nervous System (CNS). It is the most common non traumatic cause of neurologic disability in early to middle adulthood ***(Saidah et al., 2012).*** The overall incidence rate of MS in the world is 3.6 cases per 100,000 person-years in women and 2.0 in men. It is estimated to affect 2.1 million people worldwide ***(National MS Society, 2009)***

There are four clinical phenotypes of MS. Initially, more than 80% of individuals with MS experience a relapsing-remitting disease course (RRMS) characterized by clinical exacerbations of neurologic symptoms followed by complete or incomplete remission. After 10 to 20 years, or median age of 39.1 years, about half of them gradually accumulate irreversible neurologic deficits with or without clinical relapses, which is known as secondary progressive MS (SPMS). Another 10% to 20% of individuals with MS are diagnosed with primary progressive MS (PPMS), clinically defined as a disease course without any clinical attacks or remission from onset ***(He et al., 2012).***

Growing evidence supports an inflammatory pathology occurring during the early relapsing stage of MS, and neurodegenerative pathology dominates the later progressive stage of the disease. The symptoms of MS can restrict the individual's physical activity and income-earning ability, resulting in a major financial burden on the patient, family,

health system and society. Increases in disease severity are associated with both impairment in quality of life and increased costs. Direct medical costs are mainly due to relapses and pharmacological treatments in the earlier stages of disease; indirect costs are mainly due to disability and productivity loss in the later stages ***(Naci et al., 2010).***

However, the cause of MS remains unknown ***(Goodin, 2014).*** MS is largely viewed as an immune mediated disease that is initiated when a genetically susceptible individual is exposed to environmental risk factors, resulting in a dysregulated immune response targeted at the CNS ***(Verhey et al., 2013).*** The risk of developing MS is associated with certain class I and class II alleles of the major histocompatibility complex (MHC), particularly the histocompatibility leucocytic antigen-DRB1 (HLA-DRB1) locus ***(International Multiple Sclerosis Genetics Consortium (IMSGC) et al., 2011).*** A family history of MS increases the risk of MS in their siblings ***(Banwell et al., 2007b).*** If both parents are affected the risk in their children is 10 times that of the general population ***(Milo et al., 2010).*** In identical twins, both are affected about 30% of the time, while around 5% for non-identical twins and 2.5% of siblings are affected ***(Hassan-Smith and Douglas, 2011).***

Many environmental risk factors have already been proposed for MS. The incidence and prevalence of MS varies geographically ***(Simpson et al., 2011).*** Persons migrating from a high- to low-risk area after the age of puberty are thought to carry their former high risk with them, while those that migrate

during childhood seem to have the risk associated with the new area to which they migrated ***(Koch et al., 2010).*** Vitamin D insufficiency is associated with increased risk for MS development and increased disease activity especially in pediatric population in developmental ages ***(Munger et al., 2009).*** Data suggest that smokers have an increased risk of MS, which also seems to increase with cumulative dose ***(Ascherio et al., 2012).*** Moreover, Smoking may also be a risk factor for disease progression ***(Manouchehrinia et al., 2013).*** The United States Centers for Disease Control and Prevention (CDC) investigated the possibility of role of hepatitis B vaccine in development of MS and concluded that the weight of the available scientific evidence does not support the suggestion that hepatitis B vaccine causes or worsens MS ***(CDC, 2010).***

Many viruses were suggested to influence MS susceptibility, most important is the Epstein-Barr virus (EBV), which causes infectious mononucleosis ***(Bagert et al., 2009).*** There is conflicting evidence concerning the presence of EBV in brain tissue of patients with MS ***(Tzartos et al., 2012).*** EBV seropositivity among adult MS patients is near 100 percent, significantly higher than healthy controls ***(Levin et al., 2010).*** Evidence of an etiologic role for EBV in MS may be stronger in the pediatric than the adult population. ***Banwell et al. (2007a)*** found that serologic evidence for remote EBV infection was significantly higher in children with MS compared with age-matched controls (86 versus 64 percent).

AIM OF THE WORK

To detect the presence of the serum Epstein-Barr virus antibody in patients with multiple sclerosis in order to investigate EBV as a possible risk factor for RRMS and to study the association between seropositivity of anti-EBV-CA (capsid antigen) antibodies and clinical & radiological features of the disease in a sample of Egyptian patients.

DEFINITION OF MS

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease of unknown cause characterized by chronic inflammation drives multifocal demyelination of axons in both white and gray matter in the CNS ***(Khaibullin et al., 2017).*** It is the leading non-traumatic cause of disability in young adult ***(Ayache et al., 2017).***

MS is largely viewed as an immune mediated disease that is initiated when a genetically susceptible individual is exposed to environmental risk factors, resulting in a dysregulated immune response targeted at the CNS ***(Verhey et al., 2013).*** These events result in recurring episodes of inflammatory demyelination and, in many cases, a progressive neurodegenerative process ***(Patsopoulos et al., 2011).***

It typically striking adults during the primary productive time of their life. The symptoms of MS can restrict the individual's physical activity and income-earning ability, resulting in a major financial burden on the patient, family, health system and society ***(Naci et al., 2014).***

It is characterized by the destruction of the myelin sheath and inhibition of nerve impulses, eventually resulting in loss of motor function and a high level of disability. In addition to being associated with impaired mobility, MS affects quality of life, causing fatigue, pain, swallowing and breathing problems,

cognitive impairment, hearing and vision problems, and sexual dysfunction ***(Dashputre et al., 2017).***

MS affects women more frequently than men, with a ratio of 2-3:1 in around 85% of cases ***(Tur and Thompson, 2015).*** The female to male ratio is 4:1 at adolescence, 2.5:1 in adults until age 45 to 49, and then 1:1.5 after age 50 ***(Cossburn et al., 2012);*** which may be indicative of a hormonal influence on MS risk or a gender defined genetic influence on immunologic activity.

Clinical features of MS are variable; in a Brazilian study among the initial presentation, there was a predominance of motor impairment (38%) and brainstem/cerebellum (22.5%) ***(Ferreira et al., 2008). Peña et al. (2012)*** found a high rate of motor impairment and brainstem/cerebellum signs at disease manifestation about 30% each, followed by sensory symptoms and optic neuritis (10%). In addition, headache was seen in about 25% of patients at onset.

In 2013, a global survey by multiple sclerosis international federation (MSIF) found that the most common presenting symptoms of MS were sensory (40%) and motor (39%), and the least common were pain (15%) and cognitive issues (10%) ***(MSIF, 2013).*** While monofocal presentations are more common in adolescents and adults, children typically present with polyfocal symptoms ***(Yeh et al., 2009; Vaknin-Dembinsky and Karussis, 2014).***

MS starts with an acute neurological episode, a clinically isolated syndrome, which is considered to be the first clinical episode of RRMS. Clinical relapses in RRMS reflect acute inflammation in the CNS, resulting in specific clinical syndromes including optic neuritis, myelitis, brainstem/cerebellum syndrome and supratentorial syndrome. In progressive MS, progression generally presents with gradual loss of power in the lower limbs, which may be asymmetric. It is often accompanied by sensory disturbances in the lower limbs, bladder and bowel symptoms. Investigations need to rule out conditions that can mimic an inflammatory- demyelinating disease of the CNS and determine the presence of dissemination in space and dissemination in time of the inflammatory-demyelinating disease. There is no confirmatory test for MS and it remains essentially a clinical diagnosis ***(Tur and Thompson, 2015).***

The latest definition of MS phenotypes by the Committee composed by the US National MS Society, the European Committee for Treatment and Research in MS and the MS Phenotype Group, identifies the following MS courses ***(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.

- The relapsing-remitting course was showed in the previous Committee convention as “disease relapses with full recovery or with sequelae and residual deficit upon recovery” in the lack of disease progression and a relapse as “acute worsening of neurologic function followed by a variable degree of recovery, with a stable disease course between attacks

- The secondary progressive MS (SPMS) is characterized “by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course”.

- The primary progressive MS (PPMS) course is defined by the Committee of 1996 as “disease progression from the onset, with occasional plateaus and temporary minor improvements allowed”.

RRMS is the most common disease course and is seen in 85% of all cases at initial diagnosis. Individuals diagnosed with RRMS transition to SPMS, with 50% transitioning within 10 years and 90% transitioning within 25 years of RRMS diagnosis. PPMS is seen in 15% of individuals diagnosed with MS ***(National Multiple Sclerosis Society, 2017).***

There is another phenotype which is progressive relapsing MS (PRMS) which is a rare form that initially presents as PPMS; however, during the course of the disease, these individuals develop true neurologic exacerbations ***(Tullman et al., 2004).*** PPMS are distinct from those of other clinical MS phenotypes where the age of onset is typically around age 40 years and thus significantly later than that of RR-MS ***(Bashir and Whitaker, 1999).***

EPIDEMIOLOGY OF MS

The distribution and frequency of MS are assessed by estimates of prevalence and incidence. These measures provide essential information for health service planning, and can be used to monitor or reveal spatial, temporal and demographic differences in the distribution of disease. Comparisons of incidence and prevalence in different populations support assessments of the relative contribution of genetic and environmental factors in MS etiology ***(Poser and Brinar , 2007).***

The prevalence of MS is not homogenous in the world. It varies greatly between northern and southern countries. There are gradients at the country level: the prevalence increases from south to north in Japan and Europe, and from north to south in Australia and South America. Despite these variations in many geographical areas, the association of prevalence and latitude is contested by several studies. Such comparisons are limited by the heterogeneity of the diagnostic criteria used for selecting cases, population characteristics, geographical scale, methodological design and statistical methods. Thus, the notion of a gradient could be due to methodological artifacts ***(Pivot et al., 2016).***

An almost universal increase in prevalence and incidence of MS over time with a general increase in the incidence of MS in females has been observed in meta-analyses of studies on MS epidemiology since 1965 ***(Koch-Henriksen and Sørensen,***

2010). The MS Foundation reports an estimated prevalence of 400,000 people in the United States, with over 2.5 million people affected globally. MS is typically diagnosed between the ages of 20-40 years, and women are twice as likely as men to be affected by the disease ***(Dashputre et al., 2017).***

A global survey in 2013 by Multiple Sclerosis International Federation (MSIF) found that the estimated number of people with MS has increased from 2.1 million in 2008 to 2.3 million in 2013 and MS is present in all regions of the world while its prevalence vary greatly, being highest in North America and Europe and Lowest in Sub-saharan Africa and East Asia. Prevalence also varies considerably within regions. For example the highest prevalence in Europe is in Sweden, and the lowest is in Albania ***(MSIF, 2013).***

In 2013, MSIF survey also found that there were an estimated 7,000 people under 18 years with MS in the 34 countries that provided data, mainly in Europe, Eastern Mediterranean and North America ***(MSIF, 2013)*** as shown in **(Figure 1).**

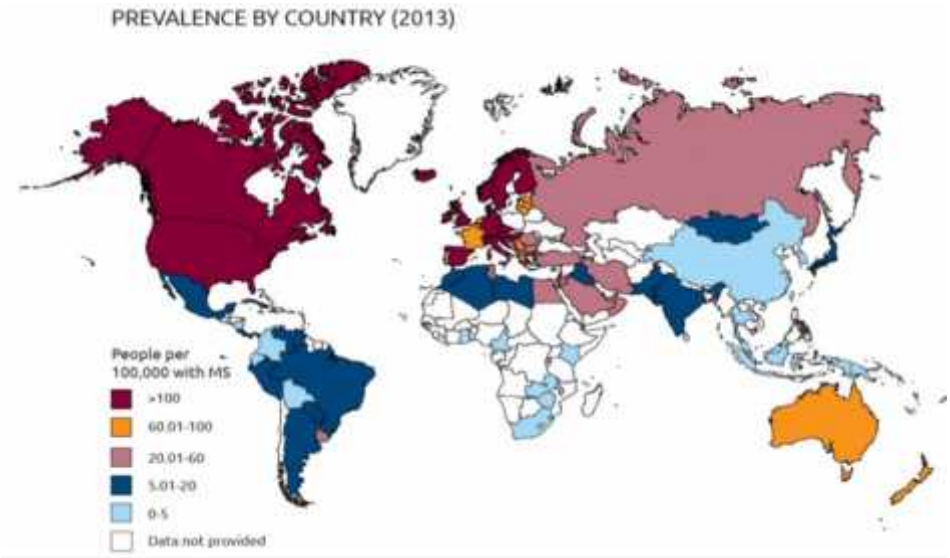

Figure (1): Prevalence of Multiple sclerosis by country ***(MSIF, 2013).***

More than 400,000 people in the United States and about 2.5 million people around the world have MS. The incidence of MS is also higher in colder climates. People of Northern European descent have the highest risk of developing MS, no matter where they live. The lowest risk appears to be among Native Americans, Africans, and Asians while Middle Eastern and North African countries are located in a low- to moderate-risk zone for MS based on the 2013 MS Atlas ***(Browne et al., 2014a).*** However, recent studies suggest a moderate-to-high prevalence in areas within this region, with an increase in the incidence and prevalence especially among women ***(Heydarpour et al., 2015).***

The most recent study pertains to the prevalence of MS among immigrants in Norway, and reported a prevalence of

162/100,000 people among the first generation of Iranians, which was markedly higher than the prevalence of MS in Iran and not significantly different from that in the total Norwegian population. Iran has the highest prevalence of MS in the Middle East and Asia. Rate of emigration has been significantly raised among Iranians and though, multiple studies have been published on prevalence of MS among Iranian emigrants ***(Nasr et al., 2016).***

Alshubaili et al. (2005) reported that the MS incidence rate has increased from 1.05 in 1993 to 2.62/100,000 in 2000. An increasing pattern was also observed in the prevalence rates (6.68/100,000 at the end of 1993 to 14.77/100,000 by 2000). The estimated prevalence was markedly higher for Kuwaitis (31.15) than for non-Kuwaitis (5.55).

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 14.1/100,000.9 ***(Hashem et al., 2010).***

A community-based survey in Al Quseir, Egypt, has found an MS prevalence of 13.74/100,000. A retrospective meta-analysis in different referral centers of Egypt has found 648 patients with definite MS. The most frequent presenting symptom

was weakness (57%), followed by sensory symptoms (19.9%), visual symptoms (15.9%), and ataxia (15.8%). 73.45% of these patients had a relapsing-remitting course, primary-progressive course was seen in 17% of patients, and 9.55% had the secondary-progressive course ***(El-Tallawy et al., 2016).***

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).***

The MS prevalence ratio of women to men has increased markedly during the last decades (2.3–3.5:1), which indicates a true increase in MS among women but not men ***(Wallin et al., 2012).*** This rapid increase probably reflects unidentified changes in the environment or nutrition. Interestingly, the predominance in women varies with latitude ***(Kampman et al., 2013; Trojano et al., 2012).*** The effect of sex on clinical features of MS is not as clear as the effect on MS prevalence; however, there is evidence that women generally have an earlier onset of disease, they have a slightly lower prevalence of primary progressive disease course and show in general less progression of disability than men ***(Bergamaschi, 2007).***

Across all of Europe, the prevalence of MS is higher in females, with a female: male ratio of 1.1–3.4. An increasing incidence of MS in women (particularly RRMS) is part of a

changing geoepidemiology of MS ***(Trojano et al., 2012)***. The underlying reason for this remains to be determined, but vitamin D deficiency has been proposed as one of the most biologically plausible explanations ***(Sellner et al., 2011).***

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 et al., 2014a).***