INTRODUCTION

Multiple sclerosis is a chronic inflammatory brain and spinal cord disease, and one of the commonest neurological diseases in young people. An interaction of environmental and genetic factors is proposed to explain geographic variation, and latitude is a well established factor: increased distance from the equator increases the prevalence of the disease ***(Ascherio et al., 2004).***

The prevalence rates estimated for Scotland and its offshore islands over the last 25 years range from 145 to 193 per 100.000 and are the highest so far detected anywhere in the world for large populations. In England and Wales, prevalence rates have varied from 74 to 112 per 100 000 in the last 15 years ***(Kurtzke and Heltberg, 2001).***

In relapsing remittent and secondary progressive types, it affects women more than men; the female to male ratio is about 2:1. Whereas the onset of multiple sclerosis in woman tends to be early (ages 18 to 30), the onset in men tends to be later in life (ages 30 to 40). While in primary progressive type has a different sex ratio from other forms of the disease. Men are as much at risk of getting primary progressive as women ***(Lucchinetti et al., 2000)***.

Relapsing remittent multiple sclerosis is presumed to be a predominantly T cell driven autoimmune disease against components of the myelin sheath ***(Hafler, 2004)***. Although the occurrence of intrathecal oligoclonal bands suggests that B cells may also be important in this condition resulting in destruction of oligodendrocytes with demyelination of axons ***(Frohman et al., 2006).***

In principal, people with multiple sclerosis can experience partial or complete loss of any function that is

controlled by the central nervous system depending on which areas are affected and how badly they are damaged ***(Lucchinetti et al., 2000)***.

The diagnoses of multiple sclerosis may be difficult as its signs and symptoms may be similar to many other medical problems. Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process for practicing physicians. Currently, the McDonald criteria focus on a demonstration with clinical, laboratory and radiologic data of the dissemination of lesions in time and space ***(McDonald et al., 2001).*** It is proposed that the 2010 revision to the McDonald criteria should be used for research or drug trials and comprises two categories: 'MS' and 'Not MS'. McDonald 2010 could be used optionally for routine clinical purposes ***(Gafson et al., 2012).***

Multimodal evoked potentials have been performed for patients with multiple sclerosis and have diagnostic and prognostic value in detection of formed plaques and in silent changes of the sensory pathways. Previous studies showed different percentages of abnormal findings of evoked potentials in patients with probable and definitive forms of multiple sclerosis. Visual evoked potentials demonstrated the highest degree of abnormal findings, followed by somatosensory and brain stem auditory evoked potentials ***(Djuric et al., 2005) .***

The susceptibility of various populations to multiple sclerosis and the clinical patterns of the disease are thought to be different. Nineteen articles related to incidence, prevalence and clinical patterns of multiple sclerosis in Arab populations were done. Data were only available for the Kuwaiti, Jordanian, Libyan, Saudi, Iraqi, Palestinian, and Omani populations. The publications ranged from 1975 to 2007 ***(Benamer et al., 2009).***

In Egypt there was a study done in Cairo University showed that the prevalence of multiple sclerosis among neurological patients was 1.41 in 1000 neurological patients (141 per 100000). and sex ratio between female to male 1.6:1, the age of onset in female was 27.79 ± 7.99 and in male 29.02 ± 2.63, and the first clinical presentation varied as motor weakness 57%, sensory 19.9%, visual 15.9%, ataxia 15.8 and the least is sphincteric manifestations, Also it showed that the ratio between different courses as relapsing remittent is 73.45%, primary progressive is 17%, secondary progressive is 9.55%. MRI finding showed classical demyelination in the periventricular white matter 80%, cerebellum 48.7%, and brainstem 53%, cervical spinal cord 10.7%, dorsal spinal cord 3.1% and ventricular dilatation 22% ***(Hashim et al., 2010).***

Another study done in Iraq of 300 multiple sclerosis patients (164 females, 136 males) with a mean age of onset being 29.2 ± 7.8 years and the duration of disease is 8.6 ± 5.9 years. Initial symptom was reported as motor in 31.7%, sensory in 28.3%, optic nerve in 24% and brainstem or cerebellar in 22.3% of patients. The course was relapsing remittent in 66.3% patients, secondary progressive in 18.7% and primary progressive in 15% patients. MRI was performed for 278 (92.6%) patients and abnormalities suggestive of multiple sclerosis were found in 266 (95.7%) patients. Visual evoked potentials was performed for 276 (92%) patients in whom abnormalities were reported in 223 (80.8 %) and two-third of these were bilateral ***(Al Araji et al., 2005).***

Another study done in Lebanon included 202 multiple sclerosis patients showed that the peak age of onset of multiple sclerosis in the third decade with 62.4% of patients developing their first symptoms between 20 and 39 years. The female/male ratio was 1.8:1.0. A positive family history

for MS was present in 5% of patients. The most frequent presenting symptoms were brainstem-cerebellar (46.2%) followed by sensory (42.5%), motor (33.9%) and visual (29.6%). Evoked potentials were performed showed that Visual, brain stem auditory and somatosensory were abnormal in 65.6%, 27.8%, and 50.7% of patients tested respectively. Also there was 194 patients were examined by MRI with 71 of them tested for both brain and spine and 121 patients for brain and 2 patients for spine only. Among patients who performed both brain and spinal MRI's, 75% showed abnormal brain and spinal MRI's, 21% had abnormal brain only, and 3% had abnormal spine only with the rest (1%) showing normal findings ***(Yamout et al., 2008).***

AIM OF THE WORK

The aim of the study is to determine the distribution of the presenting manifestation of multiple sclerosis as regard demographic data, clinical presentation and their correlation with radiological and visual evoked potential in a sample of Egyptian patients attending Ain Shams University hospitals.

Definition, Etiology and Epidemiology

Definition :

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, which results in the formation of focal demyelinated plaques in the white matter with partial axonal preservation ***(Lassmann et al., 2007).*** In most patients disease starts with a relapsing remitting course, which is followed by a secondary progressive phase. In patients with primary progressive disease the relapsing stage of the disease is missed and patients show disease progression from the onset ***(Lublin et al., 1996).*** It is generally believed that inflammation starts the disease and drives demyelination and neurodegeneration ***(Hohlfeld et al., 2004).***

There are four clinical forms of MS: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR) MS. Patients having a single bout of disease but not yet diagnosed with MS are referred to as clinically isolated syndromes (CIS), which is considered the first manifestation of the disease. RRMS and SPMS clinical forms account for approximately 80%–85% of patients, and SPMS usually evolves from RRMS. The triggers for transition from the more inflammatory and treatment-responsive RRMS clinical form to the more neurodegenerative and treatment resistant SPMS form are unknown. The PPMS form is characterized by a progressive course from the beginning without superimposed relapses and is totally refractory to available therapies ***(Compston et al., 2008).***

Etiology of Multiple Sclerosis:

MS belongs to the large group of multifactorial disorders which are believed to arise from complex

interactions of both environmental and genetic factors (Fig.1). Typical features for complex genetic diseases include modest heritability without a classic Mendelian mode of transmission and heterogeneity, which means that variation in a large number of genes contributes to the overall susceptibility. Gene/gene interactions (so-called epistatic effects) are also believed to play an important role for the pathogenesis of complex diseases ***(Oksenberg et al., 2008).***

Twin studies have revealed higher concordance rates (~25-30%) in monozygotic twins as compared with dizygotic twins (~5%), suggesting a strong genetic component. On the other hand, concordance rates of only ~30% in monozygotic twins that share identical genomes indicate that additional factors also play an important role in the susceptibility to disease ***(Hawkes et al., 2009).***

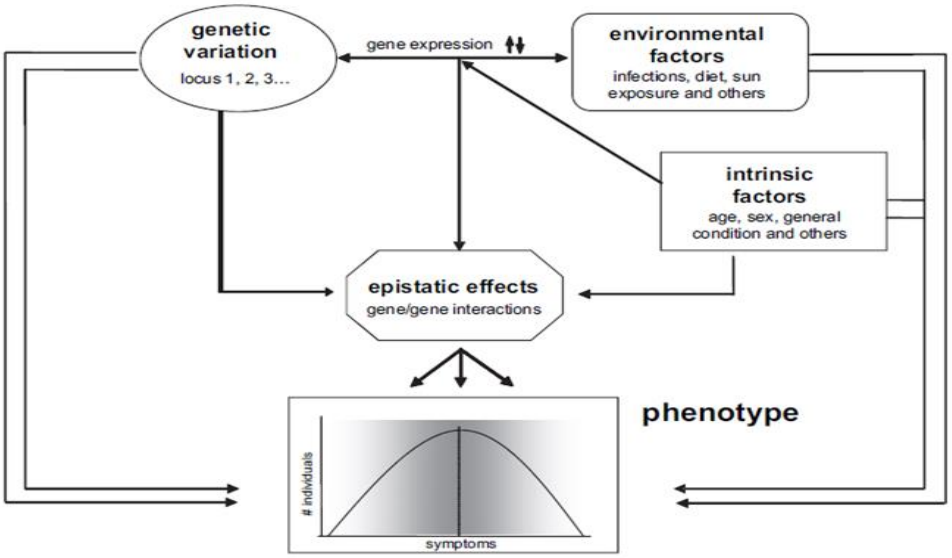

Figure (1): Schematic diagram of complex pathogenesis of multifactorial disease such as multiple sclerosis. Disease susceptibility as well as phenotypic representation is presumably influenced by variation of numerous genes in complex interaction with environmental factor. Additionally epistatic effect (gene gene interaction) and intrinsic factor of respective individuals are also believed to play important role for pathogenesis ***(Sabine et al., 2010).***

Maternal versus paternal transmission:

Several genetic epidemiological studies in MS families have indicated a skewed maternal transmission of MS ***(Ebers et al., 2004 &Herrera et al., 2008).*** However, another study on patients with affected parents, the quite opposite finding of paternal transmission has been presented ***(Herrera et al., 2007)***. The likely explanation for such discrepancies is that more than one mechanism is at stake. Opposing transmission models (maternal versus paternal) in individual families could be diluted by inclusion of many small families ***(Ilse et al., 2011).***

The inheritance of MS could be the result of several mechanisms. These may operate differently in alternative inheritance models for MS: genetic as well as environmental, or both. One of the possible genetic mechanisms is a threshold effect due to an increased number of penetrant susceptibility genes in a given parental lineage. Another possibility is the involvement of epigenetic mechanisms in disease transmission by the affected parent. Epigenesis means that there are chromatin and deoxyribonucleic acid (DNA) modifications affecting gene expression. These modifications are transmitted through cell division, but do not influence the underlying DNA sequence of that person. If epigenesist occur early in life, it can affect the availability of the critical gene product or modify the risk associated with a given gene polymorphism. Epigenetic effects do not have to occur in all cells from one person, they can also operate only in the cells of specific tissues. The threshold and epigenetic mechanisms could also occur in conjunction, especially in complex disorders as MS ***(Ilse et al., 2011)***.

Identifying susceptibility genes for complex diseases, such as MS, have been a major challenge in the past two decades. Linkage scans for MS have been performed in many

populations from different ethnicities ***(Fernald et al., 2005)***. The only region that was consistently linked to MS with statistical levels reaching genome-wide significance was the human leukocyte antigen (HLA) region on chromosome 6p21.3. Estimations revealed that the HLA region accounts for ~20-60% of genetic susceptibility in MS ***(Haines et al., 1998)***.

In almost all populations studied, an association was seen for the DRB1*1501 allele, residing on a large, extended haplo type. Yet, the complex architecture of the HLA region, with a high degree of linkage disequilibrium (LD) and large haplo type blocks, makes it difficult to pin-point the causative gene(s) or variation(s) in this region. Nevertheless, before genome-wide association studies (GWAS), the HLA region comprised the only indisputable susceptibility region linked to MS ***(Hoffjan et al., 2010).***

Environmental factors:

Several environmental factors have been proposed to influence the risk of MS, including, for example, viral infections, geographical distribution, diet and exposure to sunlight, although the link of any of these factors to the pathogenesis of disease is still under dispute ***(Oksenberg et al., 2008).***

From the very early days of MS discovery, infections have been proposed to be the underlying causes of disease initiation. Pierre Marie, a former student of Jean-Martin Charcot, who first described multiple sclerosis as a clinical entity in 1868, strongly argued that infectious pathogens, or more likely combined infections, initiate MS ***(Charot, 1868 & Marie, 1884).***

Epstein Barr virus (EBV):

Among the large list of proposed pathogens, including various herpes viruses, varicella zoster virus, human

endogenous retroviruses, Torque teno virus, Chlamydia and other bacterial agents, (EBV) has gained the most notable scientific interest to date. In the industrialized world, about 50% of the population acquires EBV between 1 and 5 years of age, while another large percentage contracts the virus during adolescence ***(Luzuriaga et al., 2010).***

For about 30–50% of individuals who acquire the virus in the second decade or later in life, the virus would lead to symptomatic primary infection known as infectious mononucleosis (IM) that is characterized by glandular fever and massive expansion of virus-specific T lymphocytes that subside with the resolving of the infection ***(Luzuriaga et al., 2010).***

Interestingly, compelling evidence support the association of IM with elevated risk of MS occurrence ***(Levin et al., 2010).*** Based on a recent updated meta-analysis evaluating a total of 18 clinical studies, the combined relative risk for development of MS after IM was estimated two fold compared to seven fold increased risk of developing the disease while when analyzed in HLA-DRB1*15 carriers individuals with history of IM ***(Nielsen et al., 2009 &Handel et al., 2010).***

A multitude of epidemiological studies conducted in the past 30 years revealed that MS patients are almost universally, 99.5%, seropositive for EBV infection, compared to matched healthy controls that have EBV seropositive of 94.2% ***(Goodin, 2009)***. This difference in seropositivity is even more pronounced in pediatric MS cases which have been shown to carry 83% seropositive compared to only 42% in matched healthy controls, while no significant difference was observed for other viruses such as CMV, parvovirus B19 and varicella zoster. Even though, these observations suggest that EBV plays a role in MS predispositions, EBV infection is not a prerequisite for

disease development since a substantial fraction of children with MS is seronegative for EBV ***(Alotaibi, 2004).***

EBV encoded nuclear antigen-1 (EBNA1) is the only EBV encoded antigen that is consistently expressed in proliferating EBV-infected memory B cells and CD4+ T lymphocytes are thought to play an important role in the immune control of persistent EBV infection. While healthy EBV-carriers preferentially recognize multiple epitopes within the central part of the immunogenic domain of EBNA1, MS patients have been shown to have significantly elevated EBNA1-specific CD4+ T cell frequencies targeting a much larger number of epitopes within this region. EBNA1-specific CD4+ T lymphocytes, but not T cell specific for other lytic or latent EBV and CMV peptides, were observed to have a higher proliferative capacity and enhanced IFNγ secretion ***(Lunemann et al., 2006).***

It is tempting to hypothesize that molecular mimicry enables EBNA1-specific T cells to cross-recognize self-autoantigens that would eventually lead to the initiation and maintenance of autoimmune pathologies. In support of this hypothesis, one study showed that MS patients present with selective elevation of EBNA1-specific T cells response that recognize more frequently myelin antigen than other non-MS-associated autoantigens ***(Lunemann et al., 2008).***

Another hypothetical mechanism of how EBV could trigger autoimmunity is based on its ability to infect and immortalize B cells by mimicking T-cell help and B-cell receptor signaling. Therefore, it is tempting to speculate that EBV could potentially infect and immortalize autoreactive B cells that contribute to disease pathology ***(Thorley-Lawson, 2001).***

Human herpesvirus-6 (HHV-6):

Another ubiquitous herpes virus that has gained relative popularity as potentially associated with MS is the

(HHV-6). It is characterized by phases of latency and reactivation that bear similarity to relapsing-remitting MS. The virus has neurotropic potential and was reported to infect oligodendrocytes and microglia cells ***(Albright et al., 1998),*** as well as to establish latency in CNS tissue which serves as a reservoir of persistent infection ***(Chan et al., 1999).***

Another aspect that strengthens the hypothesized involvement of the virus in MS is the observation that primary HHV-6 infection may lead to severe neurological complications such as encephalitis and epilepsy. Besides being able to infect neural cell, HHV-6 most commonly establishes infection in T lymphocytes and exerts modulatory effects on the immune system ***(Dockrell et al., 1999).***

Various studies in the past 25 years have investigated HHV-6 association with MS. HHV-6 has been detected in serum, CSF as well as in brain tissue and more predominantly in MS lesions as reported by some studies ***(Kim et al., 2000 & Opsahl et al., 2005)***, yet contradicted by others ***(Mirandola et al., 1999).***

Besides direct cytopathic effect, other putative mechanisms of HHV-6 involvement in MS pathology include bystander activation, and molecular mimicry. The later of which has gained compelling evidence. Myelin basic protein (MBP), a suspected target of autoreactive in MS, has been determined to share sequence homology with HHV-6 encoded U24 protein. Cross-reactive T cells responding both to MBP and U24 peptides were elevated in MS patients compared to controls ***(Tejada-Simon et al., 2003).***

So far, there is no epidemiological evidence that symptomatic HHV-6 infection increases the risk for development of MS and there is no data that would unequivocally support an etiologic role of HHV-6 in the pathogenesis of MS. However, the neuro and lymphotropic

potential of virus suggests that bystander reactivation of HHV-6 could potentially augment CNS inflammation ***(Ramagopalan et al 2009).***

Varicella-zoster virus (VZV):

It is a ubiquitous pathogen that establishes latency in the dorsal ganglia in about 95% of adults ***(Barnes et al 1986).*** It is the causative agent of varicella (chickenpox), and can occasionally lead to symptomatic reactivation known as zoster ***(Tenser et al 1984).*** Numerous epidemiological studies have investigated the link between VZV and MS, nevertheless, a meta-analysis including 40 reports conducted between 1965-1999 revealed that there is insufficient evidence to support such association ***(Marrie et al., 2001).***

Torque teno virus (TTV):

There are studies determined the specificity of clonally expanded T cells from cerebrospinal fluid (CSF) of MS patients during exacerbation and observed that these T cell clones recognized evolutionary conserved arginine- rich motifs of functional protein domains of the orphan virus (TTV). T cell clones resounded to TTV peptides as well as to peptides from other common viruses and self antigens. Therefore, it was speculated that repeated encounter, both of pathogenic or non-pathogenic infectious agents can lead to expansion of T cells responsive to conserved protein domains that are able to cross-react with ubiquitous self-antigens. These observations conclude that recurrent infections with multitude of ubiquitous pathogens rather than one particular infectious agent could be implicated in the initiation of reactivity towards self-antigens that may trigger autoimmune pathologies. However, due to the paucity of data, the relation of TTV infection and MS remains ill defined ***(Sospedra et al., 2005).***

Not only viruses and bacteria have been linked to MS, but also parasites. Helminthes are thought to have a protective role in MS among other autoimmune diseases. The prevalence of helminthes infections in countries with high sanitation standards has lead to the proposition of the hygiene hypothesis stating that regular exposure to various pathogens is required for the development of appropriate immune responses ***(Gaisford et al., 2009).***

Administration of helminthes has been shown to ameliorate disease in a mouse model of MS ***(La Flamme et al., 2003 &Walsh et al., 2009);*** while in studies has shown that when MS patients developed asymptomatic gastrointestinal infection, they experienced reduction of clinical and radiological MS activity, characterized by down modulation of proinflammatory cytokines and increase in Interleukin (IL-10) and Transforming growth factor β (TGF-β) production ***(Correale et al., 2007).***

Non-infectious environmental factors:

Vitamin D:

Among the non-infectious environmental triggers, there is a recent upsurge in studies investigating the effects of vitamin D levels on MS pathogenesis. Vitamin D is a potent immunomodulator affecting proinflammatory pathways ***(May et al., 2004),*** as well as the number and activity of regulatory T cells ***(Pierrot-Deseilligny et al., 2010).***

Epidemiological studies have shown an increase in MS frequency with increasing distance from the equator, which inversely correlates with duration and intensity of sunlight ***(Simonet al, 2010)***. Interestingly, populations situated at high latitudes but having high consumption of vitamin D rich food were observed to have reduced MS prevalence ***(Goldberg et al., 1974),*** while the risk of MS incidence decreased with movement from high to low altitudes ***(Gale et al., 1995).***

Timing of birth has also been implicated as a predictor of MS susceptibility. A study including a large data set of more than 40000 MS patients from Sweden, Denmark, Canada and Great Britain revealed that significantly fewer individuals with MS were born in November, while the incidence of MS was significantly higher for people born in May, indicating an association between prenatal sunlight and risk of MS. Interestingly, the effect of month of birth was more evident for familial cases, suggesting a potential gene/ environment interaction ***(Willer et al., 2005).***

Moreover, seasonal variations in vitamin D levels inversely correlated with gadolinium-enhancing magnetic resonance imaging lesions ***(Auer et al., 2000)*** and relapse rate ***(Tremlett et al., 2008 & Mowry et al., 2010)***. In a study investigating serum samples from 267 MS patients, it observed association of low vitamin D levels with both relapse and degree of disability as measured by EDSS (Expanded Disability Status Scale) scoring ***(Smolders et al., 2008)***.

An explanation for the beneficial effects of elevated vitamin D levels could lie in the immunomodulatory potential of the vitamin. It has been shown to affect and tolerize dendritic cells (DCs) by suppressing their pro-inflammatory cytokine secretion, expression of maturation markers, chemotaxis, and capacity to trigger proliferation of antigen- specific T cells, therefore indirectly inhibiting potentially autoreactive T cells ***(Bartels et al., 2010).***

Furthermore, since T cells themselves are described to carry vitamin D receptors (VDR), direct T cell inhibition is another hypothesized molecular mechanism of vitamin D effect on MS pathology. A recent study conducted in 2011 by Mayne on mice model of MS reported that 1,25(OH)D directly inhibits autoreactive T lymphocytes, but does not alter regulatory T cell frequencies, which bear low levels of VDR ***(Mayne et al., 2011).***