INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The etiology of MS is unknown, but it is probably the result of a complex interaction between genetic and environmental factors and the immune system ***(Tullman et al., 2013)***. In 90 % of all cases, symptoms begin between the ages of 20 and 40 ***(O'Connor et al., 2002)***.

Vitamin A or retinoic acid (RA) has important functions in the immunological response and in the CNS ***(Ross et al., 2012; Mora et al., 2008; May et al., 2004)*** in which RA acts via Retinoic acid receptors (RARs) to control plasticity and regeneration of the nervous system ***(Shearer et al., 2012).***

Vitamin A has been shown to inhibit the formation of Th17 cells, which are probably involved in the development of relapses in MS ***(Steinman et al., 2008).*** It can do sosynergistically with 1, 25-diOH-vitamin D ***(Elias et al., 2008; Schambach et al., 2007).*** A synthetic retinoid could also inhibit Th17 cell differentiation ***(Klemann et al., 2009).*** It was also found that vitamin A is possibly associated with MS risk ***(Salzer et al., 2013)*** and MRI outcomes in MS ***(Loken et al., 2012)***.

Inadequate vitamin A and RA levels result in inability to maintain tolerance and the normal balance of T cell subsets

(Iked et al., 2010). A deficiency leads to excessive or prolonged inflammatory conditions in the body ***(Ross et al., 2012).***

Others Observational studies showed that patients with MS had lower levels of plasma retinol than in healthy controls ***(Besler et al., 2002).***

The study found a statistically significant correlation between high levels of plasma retinol and improvement in patient outcome ***(Royal et al., 2002).*** RA is involved in the modulation of the normal immune response and can re-establish the balance of Th subsets and tolerogenic responses of B cells. B cells, through several pathways, play important roles in MS progression, including increasing Cell expansion, plasma cells, immunoglobulin and complement deposition. Dendritic cells contribute to the induction of Th cell polarization, depending on the cytokine environment. Vitamin a deficiency is correlated with decreasedTh2 responses while vitamin A supplementation suppresses Th1 and promotes Th2 differentiation by promotes the production of IL-10 and IL-4; IL-10 in turn enhances Th2 responses and may be suppressive for the Th1 phenotype ***(Jadidi-Niaragh and Mirshafiey, 2011; Buc, 2013; Abdolahi et al., 2015).***

About 80–90% of people with MS will initially have the relapsing–remitting form of the disease (RRMS) ***(Koch et al., 2010).*** Relapses indicate disease activity and predict disability progression, studies consistently show a correlation between

relapses in the first few years of the disease and later levels of disability ***(Scalfari et al., 2014; Stangel et al., 2015).*** Evaluating the degree of neurologic impairment in MS is by Expanded disability scale (EDSS), the multiple sclerosis severity scale (MSSS) adds the element of disease duration to the expanded disease status score (EDSS) and is designed to provide a measure of disease severity ***(Pachner et al., 2009).***

AIM OF THE WORK

The aim of the present work is:

1. Assess the level of serum vitamin A in patients with MS.
2. Compare between vitamin A level in MS patient and healthy control group.
3. Assess if level of vitamin A correlate with multiple sclerosis disability and severity.

Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized pathologically by inflammation, demyelination and primary or secondary axonal degeneration leading to formation of lesions or plaques throughout the CNS which are disseminated both in space and time ***(Trapp et al., 1998; Dutta et al., 2007).*** It is the leading cause of non-traumatic disability among young and middle aged adults in many developed countries, and it affects 2.3 million people worldwide ***(Multiple Sclerosis International Federation, 2013a).*** MS is the most common neurological disorder in young adults, especially women, usually occurring between ages 20 and 40years, it occurs before age 16 in 3–5% of all cases (early onset) ***(Biko et al., 2002)*** and in 3.4– 12.7% after age 50 (late onset). Its etiology remains unknown but is hypothesized to be due to the interaction of genetic susceptibility with predisposing environmental or viral infection factors**.** It is the most common autoimmune disorder affecting the CNS ***(Alroughani et al., 2016).*** There are four types of MS, classified by the severity of the symptoms experienced: benign, relapse-remitting, primary progressive or secondary progressive**.** People living with MS may experience periods of remissions and relapses of their symptoms. MS has a variable prognosis and studies report factors associated with worse prognosis such as: older age at onset, progressive disease

course, multiple onset symptoms, pyramidal or cerebellar symptoms and a short interval between onset and first relapse ***(Hammond et al., 2000; Khan et al., 2011).***

Epidemiology:

The epidemiology of MS is rapidly changing in many parts of the world ***(Bohlega et al., 2013),*** it had been observed, in meta-analyses of studies on MS epidemiology since 1965, an almost universal increase in prevalence and incidence overtime with a general increase in the incidence of the disease in females ***(Koch et al., 2010).*** Despite that, global information on the epidemiology of MS and the availability of resources and services for people with MS is scarce in many regions of the world, The methodology and quality of the epidemiological studies is varied, and estimates of the frequency of MS are often difficult to evaluate and compare ***(Browne et al., 2014).***

Epidemiological studies of MS have demonstrated geographic and demographic variability in both prevalence and incidence, Caucasians from Scandinavia and of Scottish origin are extremely susceptible ***(Hogancamp et al., 1997),*** while much lower prevalence in Japan and China ***(Hou et al., 1992).*** It is generally accepted that the prevalence tends to increase with increasing distance from the equator. Three distinct areas of disease frequency related to latitude were reported; High-risk areas including Northern Europe, Southern Canada and Northern USA; medium-risk areas including southern Europe,

the southern United States and Australia; and finally, low-risk areas including Asia, Alaska and Africa have been described. However this hypothesis based on latitude gradient, it is not applicable in the most methodologically adequate studies designed to make reliable comparisons between incidence rates and prevalence rates ***(Rosati et al., 1994).***

A meta-analysis of epidemiological studies published between 1980 and 1998, which standardized rates by sex and age applied to the European and the world population, found no correlation between MS frequency and latitude ***(Zivadinov et al., 2003).*** Also a systematic review reported that the latitude gradient present in older incidence studies of MS is decreasing ***(Alonso et al., 2008).***

The epidemiological studies that first documented MS registry from Egypt showed that clinical characteristics of MS in Egypt is similar to the rest of the Arab countries, and also similar to the western countries. that the female: male ratio of 2.57:1 in Egyptian patients, the peak age of onset of the disease 74% at 20–39 years, RRMS was the most common MS presentation in our population 75% ***(Zakaria et al., 2016).***

The most frequent presenting symptoms overall were motor symptoms although visual and then sensory symptoms were the two most common initial presentations of RRMS ***(Zakaria et al., 2016)***. A motor presentation was also most

commonly found in some other Arab countries such as Jordan, KSA and Dubai ***(El Salem et al., 2006; Inshasi et al., 2011).***

Etiology of Multiple Sclerosis:

The leading hypothesis of the etiology of MS is that it is a result of an autoimmune attack on the CNS ***(Compston et al., 2008),*** an unknown factor, either foreign, for example, a virus, or native to the body stimulates a population of self-reactive T cells in the peripheral circulation. The self-reactive T cells target some component of the CNS, functionally necessary for the integrity of the myelin sheath that insulates CNS neurons and the process of demyelination is initiated ***(Korn et al., 2008).***

Support for the autoimmune model includes studies that show auto reactive T cells against myelin in the peripheral circulation of MS patients ***(Pette et al., 1990),*** an expansion and activation of myelin basic protein-specific CD4+ T cells in the periphery of patients prior to clinical relapses ***(Bielekova et al., 2000).***

Extrinsic modulators likely contribute to the autoimmune cascade of signaling and cell activation in MS. Factors such as smoking ***(Weston et al., 2015),*** low vitamin D levels ***(Behrens et al., 2016),*** female gender and the effects of pregnancy (e.g., a decrease of relapse rate during the third trimester of pregnancy and rebound in the post-partum period) suggest that toxic, nutritional, and hormonal signaling affects MS pathophysiology

(Coyle et al., 2014). Exploratory work to investigate the possible contributions of the gut micro biome to immune dysfunction in MS is also underway ***(Mielcarz et al., 2015).*** The mechanisms by which these modulating factors act are largely unknown.

- ***Genetics:***

Heritability studies reveal a genetic predisposition to developing MS, with lifetime risk increased from 0.1% in the general population to 3% for siblings and up to 25% for monozygotic twins ***(Sadovnick et al., 2002),*** similar to the 2–5% seen indizygotic twins, Linkage studies have revealed that human leukocyte antigen (HLA) alleles are associated with the largest genetic contribution to MS susceptibility ***(Ramagopalan et al., 2011).***

Early linkage and candidate gene studies established correlations between genetic variants in the major his to compatibility complex (MHC) and MS risk. The MHC, encoded by a large gene family on chromosome 6, is a set of cell surface markers that display fragments of peptides broken down by the cell, allowing the body's immune cells to distinguish self from non-self. Different populations are very heterogeneous with respect to the distribution of MHC alleles. The degree of polymorphism and linkage disequilibrium (the tendency of different alleles to distribute together) within the MHC had previously made it difficult to identify the specific

allele driving the association though recent studies have demonstrated that the allele with the largest strength of association and effect size is HLADRB1*1501 ***(IMSGC, 2013).***

The HLA-DR15 haplotype, an allelic cluster of closely linked major his to compatibility complex (MHC) class II genes, including DRB1*1501, is commonly inherited in patients with MS, and it is postulated that this cluster of alleles modulates the specificity and magnitude of antigen presentation in ways that encourage an aberrant autoimmune response ***(Alcina et al., 2012).***

Recent research has tried to identify genetic variants associated with MS risk within the maternally inherited mitochondrial genome, of particular interest because of observations that mitochondrial dysfunction may underlie the bioenergetic failure seen in MS. Finally, scientists are looking at other sources of inter-individual variability the epigenome and the gut microbiome - in the hopes of explaining MS susceptibility and, ultimately, discovering targets for intervention ***(Tranah et al., 2015).***

- ***Environmental:***

1) Infectious

An infectious etiology for MS has long been hypothesized based on the presence of various pathogenic proteins and include, most prominently, Epstein–Barr virus (EBV) as well as Chlamydia and human herpes virus 6 (HHV-6) ***(Soldan et al., 2001).***

Epstein-Barr Virus

Individuals with a history of EBV infection, or EBV-triggered acute infectious mononucleosis, stand at an increased risk to develop MS due to its effect in immune system dysregulation ***(Levin et al., 2010; Lucas et al., 2011).*** Studies found that all patients with MS have antibody against EBV, whether infection with EBV is a prerequisite for the development of MS or whether 100% seropositivity for EBV is a consequence of MS is not known ***(Wandinger et al., 2000).***

Retroviruses

The possibility that MS is infectious has been extended to the idea that the disease could be sexually transmitted. A relation between sexual permissiveness and MS prevalence has been proposed, and infection with HTLV-1, a disorder with some features in common with MS, can be transmitted sexually. The sexual transmission hypothesis could be assessed with study of patients with MS and their partners ***(Hawkes et al., 2002).***

Coronaviruses

The ability of coronaviruses to produce demyelination in experimentally infected mice has led to a few searches for human coronaviruses in MS brain. By use of in-situ hybridisation, Murray and colleagues ***(Murray et al., 1992).***

JC Virus

Polyoma JC virus is the cause of progressive multifocal leukoencephalopathy (PML), the only human demyelinating disease with a proven viral cause. The kidney is the only known site of latent infection. Studies showed that JC virus not found in patients with clinically definite MS ***(Boerman et al., 1993).***

2) Vitamin D

Regarding the global MS distribution, the latitude gradientis probably the single most recognized feature: regions fartherfrom the equator generally have higher rates of MS. Sunlight exposure and, by extension, vitamin D levels, which increase in relation to the duration and intensity of sunlight exposure, may be the primary driver of the latitude gradient. Evidence for the role of vitamin D deficiency in MS also comes from investigations of food consumption. In Scandinavia, for example, coastal fishing areas where diets are richer in vitamin D have a lower incidence of MS than inland regions ***(Kampman et al., 2008).*** Besides sunlight and vitamin D, population-based epidemiologicalstudies have looked for associations with a variety of environmental risk factors, including various infections, vaccinations, trauma, surgeries, and toxin exposures ***(Belbasis et al., 2015).***

3) Vitamin A

RA the active metabolite of vitamin A, modulates the functional balance between Th1, Th2, Th17, Tregs, B cells and dendritic cells32. RA plays a major role both in increasing tolerance and in decreasing inflammation, andRA synthesis may be manipulated by the complex cross-talk among cells during infection and inflammation ***(Hall et al., 2011).*** Specific receptors for RA, namely RXRc, can promote remyelination by acting on oligodendrocytic precursor cells ***(Huang et al., 2011).***

It has long been known that RA suppresses development of autoimmune experimental encephalitis (EAE) in rats in association with increased IL-4 levels in the animal ***(Huang et al., 2011).***

4) Smoking

Cigarette smoking increases the risk of developing autoimmune diseases and leads to worse disease evolution for patients suffering from immunological diseases ***(Costenbade et al., 2006)***. The relative risk of developing MS among smokers is almost twice that of never-smokers ***(Maghzi et al., 2011).*** Cigarette smoke is capable of increasing the expression of Fas on B and CD-4 T lymphocyte cell surfaces. Cigarette smoking is associated with decreased brain volume in people with MS ***(Kappus et al., 2016),*** as well as with higher relapse rates**,** increased disability progression**,** increased cognitive impairment ***(Ozcan et al., 2014)*** and reduced survival compared with not

smoking. Smokers are more likely to be diagnosed with PPMS or transition from RRMS to SPMS ***(Jick et al., 2015).***

5) Obesity

Individuals who were overweight or obese during childhood or adolescence have twice the risk of developing MS in adulthood ***(Munger et al., 2013).*** In fact, other autoimmune diseases are also more common in individuals who are above the proper weight ***(Harpsøe et al., 2014).*** Exposure to the so-called "Western diet", which includes high fat and cholesterol, high protein, high sugar, and excess salt intake, promotes obesity, metabolic syndrome, cardiovascular disease and autoimmune diseases. One key player in the immunological tolerance response that can be affected by obesity is regulatory T cells (Tregs). These are forkhead box P3 (FOXP3) + T cells that have pivotal importance in the mechanisms controlling immunological homeostasis and function ***(Sakaguchi et al., 2008).***

6) Diet

High salt (sodium chloride) diet has been shown to boost the induction of Th17 lymphocytes both in animal models and in humans ***(Kleinewietfeld et al., 2013)***. The Th17 cells generated under high-salt diet appear to be highly pathogenic and related to pro-inflammatory cytokines. Although still an experimental observation that needs epidemiological confirmation, it is important to alert the patients about this potentially hazardous factor ***(Wu et al., 2013).***

7) Alcohol

A dose-dependent association between alcohol consumption and the risk of developing MS has been shown recently ***(Hedström et al., 2014).*** Patients with MS seem to have a tendency to misuse alcohol, but only very few studies have been carried out on the subject ***(Beier et al., 2014).*** At least in vitro, ethanol can induce a cytokine profile consistent with a Th17 regulatory phenotype. A further complication of the long-termalcohol consumption in patients is, obviously, the cognitive alterations induce both by ethanol and MS ***(Freysdottir et al., 2011).***

Pathogenesis:

MS is an autoimmune neuro inflammatory and demyelinating disease of the CNS mediated by autoreactive T cells, B cells and monocytes against CNS proteins ***(Abdolahi et al., 2015).*** The cytokines produced by dendritic cells (DC) lead to differentiation of naive CD4+ T cells into effector T helper (Th) subsets in the lymph nodes ***(Boppana et al., 2011).*** T helper 1 cells produce and secrete proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ). Interleukin (IL) -4 activation via T cell-specific transcription factor, GATA-3, stimulates Th2 cell differentiation, which results in release of IL-4 and IL-5. T helper 17 subset cells, which are typically characterized by the production of IL17A, IL-17 F and other cytokines including IL-21, IL-22 and IL-23, are promoted by IL-1β and IL-23 ***(Jadidi-Niaragh et al., 2011; Buc et al., 2013).*** The Th17 phenotype is considered a major