INTRODUCTION

The pathological hallmarks of multiple sclerosis (MS) are focal lesions, characterized by demyelination, inflammation, axonal injury and gliosis, and diffuse axonal degeneration throughout the CNS. In some regions, MS prevalence can exceed 100 per 100 000 people, and worldwide up to 2 million people are estimated to be affected. The peak age of onset is between 20 and 40 years, and disease progression often leads to severe neurological disability ***(Pugliatti et al., 2002).***

The exact cause and pathogenesis of MS are unknown. The most widely accepted hypothesis is that MS is an autoimmune disease that leads to destruction of CNS myelin. Anti-myelin T-cell-mediated inflammatory responses are believed to have a crucial role in the development of focal lesions. However, the underlying mechanism of the widespread axonal degeneration is not yet fully understood ***(Frohman et al., 2006).***

Three types of vascular dysfunction have been described in MS. First, findings from epidemiological studies suggest that patients with MS have a higher risk for ischemic stroke than people who do not have MS. The underlying mechanism is unknown, but might involve endothelial dysfunction secondary to inflammatory disease activity and increased plasma homocysteine concentrations ***(D'haeseleeret al., 2011).***

Second, patients with MS have global cerebral hypoperfusion, which might predispose them to the development of ischemic stroke. The widespread decrease in perfusion in normal-appearing white matter and grey matter in MS seems not to be secondary to axonal degeneration, but might be a result of reduced axonal activity, reduced astrocyte energy metabolism, and perhaps increased blood concentrations of endothelin-1. Data suggest that a subtype of focal MS lesions might have an ischemic origin, and there seems to be a link between reduced white matter perfusion and cognitive dysfunction in MS ***(D'haeseleeret al., 2011).***

Third, the pathology of MS might be the consequence of a chronic state of impaired venous drainage from the CNS, for which the term chronic cerebrospinal venous insufficiency (CCSVI) has been coined. A number of recent vascular studies do not support the CCSVI theory, but some elements of CCSVI might be explained by slower cerebral venous blood flow secondary to the reduced cerebral perfusion in patients with MS compared with healthy individuals ***(Zamboni and Galeotti, 2010).***

AIM OF THE WORK

- To review the vascular abnormalities described in Multiple Sclerosis.
- To discuss the pathophysiological significance and possible mutual relations between these vascular abnormalities and Multiple Sclerosis.
- To focus on Chronic Cerebrospinal Venous Insufficiency (CCSVI) and its relation to Multiple Sclerosis as a main underlying pathological change in the vascular theory of Multiple Sclerosis.

OVERVIEW OF MULTIPLE SCLEROSIS

Multiple sclerosis (abbreviated MS, also known as disseminated sclerosis or encephalomyelitis disseminata) is a disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. Disease onset usually occurs in young adults, and it is more common in females ***(Compston and Coles 2008)***.

Epidemiology of Multiple Sclerosis

Multiple sclerosis (MS) is one of the most common diseases of the central nervous system (brain and spinal cord). The prevalence in Egypt showed a great discrepancy. In a study on hospital patients registry in 2002, the prevalence rate of MS among Egyptian population in different centers was estimated to be about 25/100.000, where in Cairo only, it was found 35/ 100.000, and in Upper Egypt it was low 1.2/100 000 **(*Hashem et al., 2010).***

Previous studies in Egypt reported that the prevalence of Multiple sclerosis in Cairo among other neurological disorders was estimated to be about 3.7% **(*Moustafa, 1954*),** where in Alexandria it was 0.5% **(*El-Garem, 1964)*** *and* ***(Kandil et al. 2006)****,* reported that multiple sclerosis patients percentage

admitted to Assuit University hospital during one year was 0.7% among other neurological patients.

Prevalence estimates for MS in the United States vary from 58 to 95 per 100,000 populations ***(Noonan et al., 2010).***

According to the National Multiple Sclerosis Society, 400,000 individuals in the United States are affected by MS, misdiagnosis is common ***(National Multiple Sclerosis Society, 2010).***

Worldwide, approximately 2.1 million people are affected by MS. The disease is seen in all parts of the world and in all races, but rates vary widely ***(National Multiple Sclerosis Society, 2010).***

In general, the prevalence of MS tends to increase with latitude (eg, lower rates in the tropics, higher rates in northern Europe), but there are many exceptions to this gradient (eg, low rates among Chinese, Japanese, and African blacks; high rates among Sardinians, Parsis, and Palestinians), which implies that racial and ethnic differences affect risk. In addition, a substantial increase in MS incidence has been reported from different regions, suggesting that environmental factors, as well as geographic and genetic ones, play an important role in MS **(*Rosati, 2001).***

Worldwide, the median estimated prevalence of MS is 30 per 100,000 (with a range of 5–80). Regionally, the median estimated prevalence of MS is greatest in Europe (80 per 100,000), followed by the Eastern Mediterranean (14.9 per 100,000), the Americas (8.3 per 100,000), the Western Pacific (5 per 100,000), South-East Asia (2.8 per 100,000) and Africa (0.3 per 100,000) **(*World Health Organization [WHO], 2008).***

Classification:

Several subtypes, or patterns of progression, have been described. Subtypes use the past course of the disease in an attempt to predict the future course. They are important not only for prognosis but also for therapeutic decisions. In 1996 the United States National Multiple Sclerosis Society standardized four subtypes' definitions ***(Reingold, 1996).***

1. Relapsing remitting,
2. Secondary progressive,
3. Primary progressive, and
4. Progressive relapsing.

The relapsing-remitting subtype is characterized by unpredictable relapses followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits suffered during attacks may either resolve or leave sequelae, the latter being more common as a function of time ***(Compston and Coles 2008)***. This describes the initial course of

85-90% of individuals with MS. When deficits always resolve between attacks, this is sometimes referred to as benign MS ***(Pottock and Rodriguez, 2008)***.

The relapsing-remitting subtype usually begins with a clinically isolated syndrome (CIS**)** ***(Miller et al., 2006)***.

CIS is an individual's first neurological episode, caused by inflammation or demyelination of nerve tissue. An episode may be monofocal, in which symptoms present at a single site in the central nervous system, or multifocal, in which multiple sites exhibit symptoms ***(Compston and Coles 2008)***.

Brain lesions associated with a clinically isolated syndrome may be indicative of multiple sclerosis (MS). In order for such a diagnosis, multiple sites in the central nervous system must present lesions, typically over multiple episodes, and for which no other diagnosis is likely. A clinically definitive diagnosis of MS is made once an MRI detects lesions in the brain, consistent with those typical of MS ***(Miller et al., 2006)***.

Secondary progressive MS (sometimes called "galloping MS") describes around 65 % of those with an initial relapsing-remitting MS, who then begin to have progressive neurologic decline between acute attacks without any definite periods of remission. Occasional relapses and minor remissions may appear ***(Compston and Coles 2008)***. The median time between disease

onset and conversion from relapsing-remitting to secondary progressive MS is 19 years ***(Rovaris et al., 2006)***.

The primary progressive subtype describes the approximately 10–15% of individuals who never have remission after their initial MS symptoms. It is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements. The age of onset for the primary progressive subtype is later than for the relapsing-remitting, but similar to mean age of progression between the relapsing-remitting and the secondary progressive. In both cases it is around 40 years of age ***(Miller and Leary, 2007)***.

Progressive relapsing MS describes those individuals who, from onset, have a steady neurologic decline but also suffer clear superimposed attacks. This is the least common of all subtypes ***(Compston and Coles 2008)***.

Atypical variants of MS with non-standard behavior have been described. These include Devic's disease, Balo concentric sclerosis, Schilder's diffuse sclerosis and Marburg multiple sclerosis; and there is debate on whether they are MS variants or different diseases. Multiple sclerosis also behaves differently in children, taking them more time to reach the progressive stage. Nevertheless they still reach it at a lower mean age than adults ***(Compston and Coles 2008)***.

Clinical Presentation of Multiple Sclerosis

The person with MS can suffer almost any neurological symptom or sign, including changes in sensation (hypoesthesia and paraesthesia), muscle weakness, muscle spasms, or difficulty in moving; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia), visual problems (nystagmus, optic neuritis, or diplopia), fatigue, acute or chronic pain, and bladder and bowel difficulties ***(Compston and Coles 2008)***. Cognitive impairment of varying degrees and emotional symptoms of depression or unstable mood are also common. Uhthoff's phenomenon, an exacerbation of extant symptoms due to an exposure to higher than usual ambient temperatures, and Lhermitte's sign, an electrical sensation that runs down the back when bending the neck, are particularly characteristic of MS although not specific. The main clinical measure of disability progression and symptom severity is the Expanded Disability Status Scale or EDSS ***(Heesen et al., 2007)***.

Symptoms of MS usually appear in episodic acute periods of worsening (called relapses, exacerbations, bouts, attacks, or "flare-ups"), in a gradually progressive deterioration of neurologic function, or in a combination of both. Multiple sclerosis relapses are often unpredictable, occurring without warning and without obvious inciting factors with a rate rarely above 1 and a half per year. Some attacks, however, are preceded by common triggers.

Relapses occur more frequently during spring and summer ***(Compston and Coles 2008)***.

Predisposing factors triggering Multiple Sclerosis

Viral infections such as the common cold, influenza, or gastroenteritis increase the risk of relapse. Stress may also trigger an attack. Pregnancy affects the susceptibility to relapse, with a lower relapse rate at each trimester of gestation. During the first few months after delivery, however, the risk of relapse is increased. Overall, pregnancy does not seem to influence long-term disability. Many potential triggers have been examined and found not to influence MS relapse rates. There is no evidence that vaccination and breast feeding, physical trauma, or Uhthoff's phenomenon are relapse triggers ***(Tataru et al., 2006)***.

Aetiopathogenesis of Multiple Sclerosis

Despite a large body of research, the aetiology of multiple sclerosis (MS) remains unclear. Recent findings document that genetic and environmental factors substantially influence the course of disease well as the chance of getting the disease. The question as to whether an immune dysregulation at the heart of the pathogenesis is the initial event or a secondary phenomenon

of the disease remains unanswered at this time ***(Ascherio and Munger, 2007).***

The Autoimmune etiology

Multiple sclerosis (MS) is the most common neurological disease in young adults (***Compston A. et al 2002***). The disease is heterogeneous in clinical appearance, and it is divided into different groups based on both clinical and radiographical data (***Polman CH, et al 2005***).

Factors responsible for the different courses of the disease are unknown and the etiology of MS remains uncertain. One of the most widely accepted hypotheses is that MS is a progressive, autoimmune, demyelinating disease of the CNS where chronic inflammation is central to the axonal injury and loss, leading to deficits of motor, autonomic, and neurocognitive function (***Charil A, et al 2007***). This autoimmune response involves T-cells, B cells, macrophages/microglia, and cytokinemediated effects against auto-antigens such as myelin basic protein (MBP), proteolipid protein, and myelin oligodendrocyte glycoprotein (***Sospedra M, et al 2005***).

Immunomodulatory therapies targeted to reduce inflammation have shown clinical benefits in MS patients (***Gunnarsson M, et al 2011***). First-line immunomodulators include Interferon-beta and Glatiramer acetate, which are used for

the treatment of relapsing remitting (RR) MS patients. Both drugs are known to modulate the immune system, reducing the annual rate of relapse and T2 lesions on the MRI scan by 30%. A newer drug, Natalizumab, which is a selective adhesion molecule inhibitor, is reserved for MS patients who do not adequately respond to first-line immunomodulatory therapies (***Mendes A, et al 2011***). Nevertheless, these modalities are less likely to benefit patients with the chronic progressive (CP) type of the disease (***Panitch H, et al 2004***).

Both genetic and environmental factors have been shown to contribute to susceptibility to MS. Among studied genes for susceptibility to MS, the genes on chromosome 6p21 in the area of the major histocompatibility complex [MHC; histocompatibility leukocyte antigen (HLA) in humans], in particular the alleles -DR and -DQ of the genes, have been shown to have strong correlations accounting for 10%–60% of the genetic risk of MS (***Haines JL, et al 1998***). The association between these susceptibility genes and autoimmunity is thought to involve their role as antigen-presenting molecules to CD4+ T cells (***Chiang YJ, et al 2000***).

This deregulation in self-recognition, which has been shown to be related to the T-cell signaling pathways, can result in epitope spreading and eventual autoimmunity (***Tuohy VK, et al 1999***).

However, studies based on the concordance rates of mono-zygotic twins show that the genetic component of MS risk is around 25% (***Willer CJ, et al 2003***), suggesting that environmental factors also contribute to MS pathogenesis. In addition, epigenetic mechanisms, including DNA methylation, histone modifications, and micro (mi)RNAs which have the ability to regulate post-transcriptional gene expression through multiple mechanisms, have been shown to account for the observed disconcordance rates of mono-zygotic twins. These epigenetic factors provide a bridge between the external environment, such as infectious agents and UV sunlight, and the individual genetic makeup, determining the initiation and the progression of MS (***Burrell AM, et al 2011***). Nevertheless, a detailed discussion of epigenetic mechanisms is beyond the scope of this review.

The Infectious etiology

Infectious agents have been suggested to be among non-genetic causes of MS. The most convincing evidence for the association between infectious agents and MS comes from the Faroe Islands MS epidemics after 1940, when British troops in the Second World War occupied the islands, which were known not to have had MS cases before (***Kurtzke JF, et al 2001***).

In addition, the oligoclonal IgG antibodies in the CSF, one of the tests used to diagnose MS, frequently show increased

antibody titer for measles, rubella, or varicella zoster (***Reiber H, et al 1998***). The results of clinical studies show benefits of treating MS patients with the antiviral agent Acyclovir (***Lycke J, et al 1997***) or with its prototype, Valaciclovir (***Friedman JE, et al 2005***), further supporting the role of infectious agents in MS pathogenesis.

Infectious agents are able to trigger autoreactive T cell responses against myelin and its components through molecular mimicry (***Wucherpfennig KW, et al 1995***). Such a molecular mimicry has been identified for the Epstein-Barr virus (EBV), a double-stranded DNA herpes virus, which has been extensively studied for its relation to MS (***Thacker EL, et al 2006***). The molecular mimicry is imparted by the existing homologies between EBNA1 (an EBV nuclear antigen) and MBP, leading to cross-reactivity between EBNA1 and antibodies against MBP (***Bray PF, et al 1992***).

In addition, due to structural similarities, strong cross-reactivity was observed between a peptide belonging to the EBV DNA polymerase, BALF5, and a peptide from MBP (***Lang HL, et al 2002***). These specific structures are recognized by the same T-cell receptor in the context of HLA DR2 haplotypes DRB1*1501 and DRB5*0101, two HLA haplotypes which are linked to predisposition to MS (***Prat E, et al 2005***).

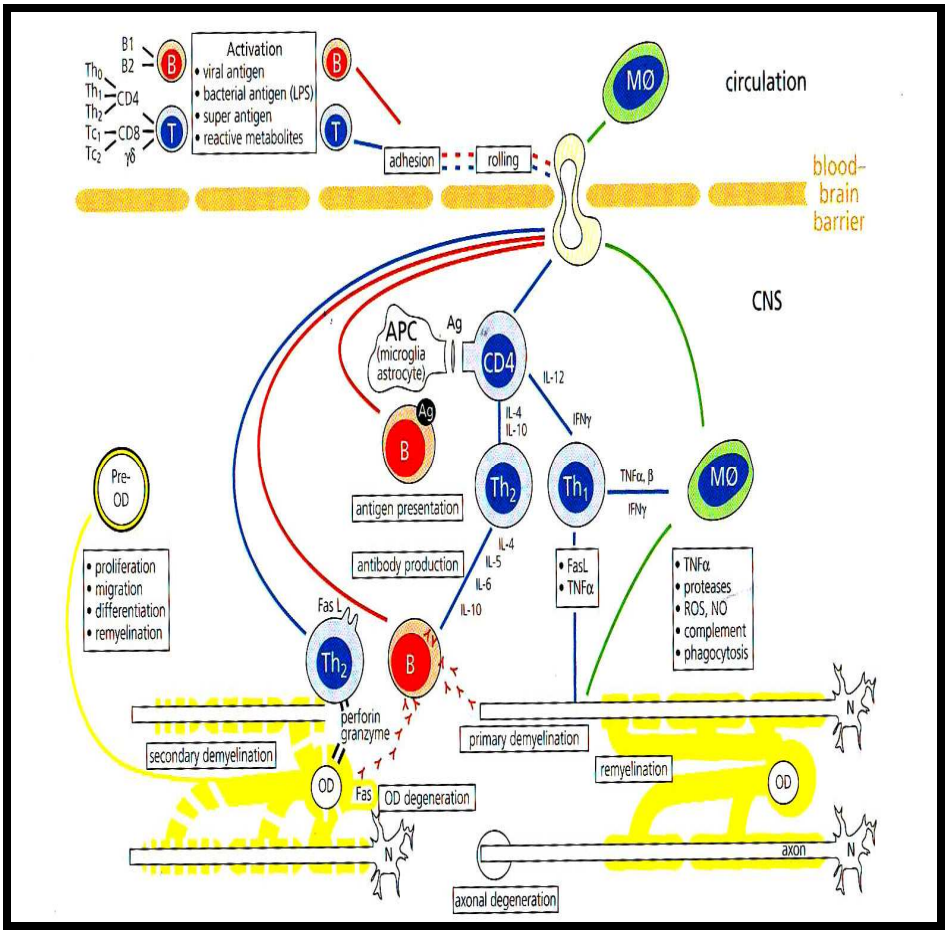

Fig. (1): Schematic illustration of factors potentially involved in the immune-mediated destruction in multiple sclerosis (MS) lesions. Abbreviations: Ag, antigen; APC, antigen-presenting cell; B, B cell; B1, B cell, fetal type; B2, B cell, adult type; Fas, CD95 molecule; FasL, Fas ligand; γδ, $\gamma\delta^{+}$T cell, fetal type; IFNγ, interferon-gamma; IL, interleukin; LP, lipopolysaccharide; MO, monocyte/ macrophage; N, neuron; NO, nitric oxide radicals; OD, oligodendrocyte; ROS, reactive oxygen species; T, T cell; Tc, cytotoxic T cell; Th, T helper cell; TNFα, tumour necrosis factor-alpha ***(Nikbin et al., 2007).***